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OF THE MEDICAL SCIENCES

MAY, 1935

ORIGINAL ARTICLES.

CLINICAL ESTIMATION AND SIGNIFICANCE OF CALCIUM-ION CONCENTRATIONS IN THE BLOOD.*†

By Franklin C. McLean, Ph.D., M.D.,
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One of the so-called physiologic constants is the concentration of calcium in the blood plasma.‡ That the maintenance of this concentration within a relatively narrow normal range is a function of the parathyroid glands has been clearly shown by the work of Collip.[1] This range is, on the average, between 10 and 11 mg. per 100 cc. for man, beef, sheep, dogs, cats and rats and somewhat higher for rabbits and guinea pigs.[2] For man, in individuals, the extremes of the normal range may be considered to be 9 and 11.5 mg. per 100 cc.[3]

Owing to a considerable interest in the behavior of calcium in the body in health and disease, the gross changes in the concentration of calcium in the serum, occurring in various clinical conditions, have received a great deal of attention. The more important find-

* Read before the Chicago Society of Internal Medicine, Jan. 28, 1935.
† This work was aided by a grant from the Josiah Macy, Jr., Foundation.
‡ While the majority of observations reported in this paper were made upon serum from coagulated blood, it has been shown that the results upon serum and upon plasma from blood prevented from coagulation, by a means which does not interfere with the ionization of calcium, are indistinguishable.

ings, with reference to which agreement is more or less general, are summarized in Table 1.

TABLE 1.—TOTAL CALCIUM IN PLASMA OR SERUM.

Elevated (12 to 16 mg. per 100 cc.).
- Hyperparathyroidism.
- Hyperproteinemia (especially multiple myeloma).
- Overdosage of viosterol.

Within or near the normal range (9 to 11.5 mg. per 100 cc.).
- Rickets.
- Osteomalacia.
- Paget's disease.
- Senile osteoporosis.
- Calcinosis universalis.
- Tetany of alkalosis.

Lowered (4 to 8.5 mg. per 100 cc.).
- Hypoparathyroidism, including parathyroid tetany.
- Hypoproteinemia.
- Hyperphosphatemia of nephritis and uremia.
- Some cases of rickets and of osteomalacia.
- Infantile tetany.

In 1913, Rona and Takahashi[1] first demonstrated that the calcium in the serum could be differentiated into two fractions, about 50% being capable of passing through a membrane impermeable to proteins, the remaining 50% remaining with the proteins of the serum. These fractions have since come to be known as diffusible and non-diffusible. They concluded that the non-diffusible fraction is bound in some way to protein, and this conclusion has been almost universally accepted. Interest has, however, centered upon the state of the diffusible calcium, known to be free in solution. Nor is this merely an academic interest, since it appears that the physiologic activity and hence the clinical importance of the calcium in the blood depend upon its physical-chemical state.

In the light of modern chemical theory the common salts of calcium in dilute aqueous solution are to be thought of as completely dissociated into calcium ions, each carrying a double positive electrical charge, and the corresponding negatively charged ions. Calcium chlorid, for example, does not exist as such in dilute solution, but each molecule dissociates into one calcium ion (Ca^{++}) and two chlorid ions (Cl^{-}). On the other hand, certain chemical substances, such as citrate, are capable of binding calcium in complex combinations, in such a way that it loses its electrical charges, certain of its chemical properties and at least certain of its physiologic activities.[5] Since Ca^{++} and calcium bound to such substances as citrate both pass freely through semipermeable membranes, diffusion methods are not of use in distinguishing between these forms.

Starting with general agreement that at least part of the diffusible calcium in serum is in the form of free Ca^{++}, and with much reason to believe that this form is of primary physiologic importance, two schools of thought, both supported by experimental evidence, have developed with reference to the state of the diffusible calcium of

the blood. One school has held that all, or very nearly all, of the calcium not bound to protein is ionized (Fig. 1, *A*). The other school, relying chiefly upon what is known concerning the solubility of calcium carbonate and calcium phosphate, has held that of approximately 5 mg. per 100 cc. of serum of the calcium not bound to protein, not more than 2 mg. can be in the ionized state. In order to account for the remaining 3 mg. a diffusible form of calcium, bound to some citrate-like substance, as yet unidentified, has been postulated, and has sometimes been called calcium-X (Fig. 1, *B*). As to cerebrospinal fluid, which contains only minute amounts of protein, and a total of about 5 mg. of calcium per 100 cc., all diffusible, the same question arises, and the same differences of opinion have existed. Although Greenberg and Greenberg[6] have recently concluded that there is no direct evidence in favor of it, most recent reviews[2,3,7,8,9] incline toward acceptance of the calcium-X hypothesis. Present thought concerning the state of calcium in the serum is summarized in Fig. 1.

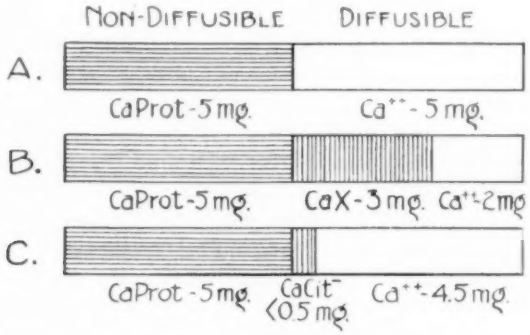

FIG. 1.—Various views of approximate distribution of calcium in normal human serum. *C* represents the findings reported in this paper. Ca^{++}, ionized calcium; CaProt, calcium bound to protein; CaX, hypothetical bound but diffusible calcium; $CaCit^{-}$, calcium bound to citrate.

In view of the uncertainty as to the conditions present in the fluids of the normal body it is not surprising that interpretation of abnormal findings has been a source of great difficulty, and of further difference of opinion. To the clinician this has meant (1) that a normal figure for the total calcium of the serum might possibly conceal an abnormal distribution between the various forms, and (2) that no sound basis has existed for clinical interpretation of abnormal fluctuations in the total calcium level.

Obviously the key to these difficulties lies in the possibility of making direct observations of Ca^{++} concentrations. Attempts to find a suitable method, by electrometric and other means, have not been lacking, but have not met with success, particularly when applied to biologic fluids. The studies here reported originated

from an attempt on the part of the authors to make a new approach to such measurements.

The method finally adopted took advantage of a familiar biologic preparation, the isolated heart of the frog, already known to be extremely sensitive, within a certain range, to changes in the calcium content of its nutrient fluid. As to the method, it was necessary to show that this sensitivity could be reduced to quantitative terms, that the preparation is adapted to biologic fluids from other species and that the sensitivity is specific for calcium in the ionized form, the preparation being indifferent to calcium bound in combination with other substances. These conditions were met, and a method which is workable and reasonably accurate resulted.[10] It is not recommended for use in the clinical laboratory, but the studies which it made possible have yielded another method of estimation of Ca^{++} concentrations, to be described, which is available for routine clinical use.

Observations by the frog heart method quickly disposed of the question of the state of calcium in the fluids of the normal human body. The Ca^{++} concentration in normal human fluids was found to be in the neighborhood of 5 mg. per 100 cc. of fluid, and this was found to be true whether cerebrospinal fluid, containing a total of 5 mg. of calcium per 100 cc., or serum, containing twice this amount, was examined. It thus appears that all or nearly all of the calcium in protein-free fluids, such as cerebrospinal fluid, is present in ionized form, and that in protein-containing fluids, such as serum, plasma, pleural fluid, and ascitic fluid, Ca^{++} and calcium bound to protein are together sufficient to account for all or almost all of the total calcium. There thus seems to be no further reason to postulate quantitatively significant amounts of a third form of calcium in the fluids of the normal human body, although it can scarcely be doubted that a small but insignificant amount of bound but diffusible calcium, corresponding to the small amounts of citrate present in human fluids, does exist in these fluids (Fig. 1, *C*).

The calcium-protein relationship was next investigated, and this study led to the discovery that the ionization of calcium, in protein-containing fluids, is determined by a chemical equilibrium between calcium and protein, and that this equilibrium can be described as a first approximation by a simple equation. The hydrogen-ion concentration also plays a part in this equilibrium, as do magnesium, citrate and the albumin to globulin ratio, but the influence of these factors, individually and collectively, is small. For the details of these relationships reference is made to a previous paper by the authors.[11]

Having shown that the distribution of calcium between Ca^{++} and calcium bound to protein depends upon the total protein present, it now became possible to calculate Ca^{++} concentrations from values for total calcium and total protein. Studies, some of which are

still in progress, made by a combination of calculation and direct observation of Ca^{++} concentrations, have led to certain conclusions, which are here presented with the reservation that they represent the basis of experience up to the present time, but that the subject is as yet by no means exhausted.

The first conclusion is that values for Ca^{++} concentrations as calculated from total calcium and total protein are in substantial agreement with values obtained from direct observation by the frog heart method. It follows, therefore, that the method of calculation, which is readily available, is reliable and trustworthy for routine clinical observations and for the purposes of differential diagnosis. The method requires only accurate analysis for the total calcium and total protein of the serum or plasma,* and thus adds no equipment to that already available in most laboratories.

The only additional tool required is a chart (Fig. 2) from which values for total calcium and total protein may be immediately translated into terms of Ca^{++}. The point of intersection of a vertical line representing total protein concentration with a horizontal line representing total calcium concentration will fall on or between diagonal lines representing Ca^{++} concentrations, and its location with reference to these lines gives at once the Ca^{++} concentration for the given conditions. A figure for calcium bound to protein, if desired, is easily derived from the chart by subtracting Ca^{++} from total calcium. An additional line, including all points at which Ca^{++} and calcium bound to protein are equal to each other, and therefore at which 50% of the total calcium is ionized, is included in the chart as a guide to the proportion of calcium which is ionized under average conditions.

Fig. 2 serves a double purpose. It is available for calculation of Ca^{++} concentrations under any given conditions, and at the same time illustrates in concise form our findings as to the state of calcium in the serum or plasma. It is constructed from the equation previously referred to, but for convenience in use is presented in terms of grams of protein and of milligrams of calcium per 100 cc. of serum. Within the range of this chart the error involved in these transformations from the original form of the equation is insignificant.

The broken diagonal lines enclose the normal range of Ca^{++} concentrations, which has been found, as a rule, to lie between 4.25 and 5.25 mg. per 100 cc. The chart shows at a glance that the same concentration of total calcium, with total protein varying,

* For total calcium we have used the method of B. Kramer and F. F. Tisdall (J. Biol. Chem., **48**, 223, 1921) as modified by E. P. Clark and J. B. Collip (J. Biol. Chem., **63**, 461, 1925). For total protein we have determined total minus non-protein nitrogen using a micro-Kjeldahl method for both (Peters, J. P., and Van Slyke, D. D.: Quantitative Chemistry, Methods, Baltimore, The Williams & Wilkins Company, p. 526, 1931) and using a factor of 6.3 to convert grams of nitrogen to grams of protein.

may result in abnormally low, normal, or abnormally high Ca^{++} concentrations. On the other hand, when total calcium and total protein vary together, while maintaining the relationship to each other expressed by the chart, the result may be a normal Ca^{++} concentration over a considerable range of variation in total calcium. Furthermore, the chart shows that when the total calcium changes, in either direction, total protein remaining constant, the Ca^{++} concentration must also change, and in a manner bearing a definite

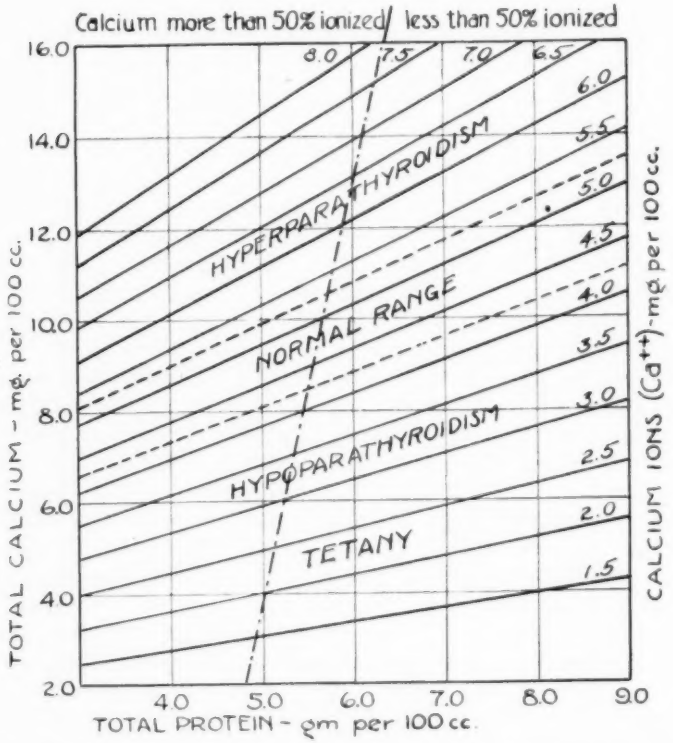

FIG. 2.—Chart for calculation of Ca^{++} concentration from total protein and total calcium of serum or plasma.

relationship to the change in total calcium. Since it is clear from the studies to be referred to that the Ca^{++} concentration is of primary physiologic and clinical importance, it follows that determination of the total calcium concentration of the serum, without simultaneous determination of the total protein, is of questionable significance.

Our findings indicate that the so-called diffusible calcium of the serum is all or nearly all ionized and that consequently the diffusible

calcium is at least a rough measure of Ca^{++} concentrations. Use of dialysis or ultrafiltration methods is, therefore, a valid clinical procedure, and the results of these methods, interpreted in the light of our findings, are in agreement with the results of the method here proposed. It must be noted, however, that these methods are difficult, time consuming and, except in expert hands, unreliable. They possess no advantages, for routine clinical use, over the simple method for calculation of Ca^{++} concentrations from total calcium and total protein.

Attention is first directed to those conditions in which there is some reason to believe that calcium is implicated in a disease process but in which the Ca^{++} concentrations have been found to be within normal limits. This applies, for example, to the more common disorders of calcification, such as rickets, Paget's disease, senile osteoporosis and calcinosis. In all of these conditions the total calcium of the plasma has been known to be at or very near the normal level. However, with the possibility of three forms of calcium, of which at least two were unknown as to quantity, there were many possibilities of variation among the unknowns. All of these possibilities have received attention and in the case of rickets the conclusion has been drawn, on the basis of adsorption experiments, that the diffusible calcium of the serum is markedly changed in composition.[12]

TABLE 2.—OBSERVED AND CALCULATED Ca^{++} CONCENTRATIONS IN SERUM.

Date, 1934.	Patient.	Total protein, gm. per 100 cc.	Total calcium, mg. per 100 cc.	Ca^{++}			Diagnosis.
				Calculated, mg. per 100 cc.	Observed, mg. per 100 cc.	Difference, mg. per 100 cc.	
4/25	L. G.	6.9	10.5	4.7	4.5	−0.2	Paget's disease.
10/16	C.	7.9	10.7	4.4	4.0	−0.4	Osteoporosis.
11/2	Z.	6.5	9.7	4.5	4.3	−0.2	Osteoporosis.
11/15	L.	7.2	10.6	4.6	4.5	−0.1	Calcinosis universalis.
12/6	McC.	7.1	10.5	4.6	4.3	−0.3	Calcinosis universalis.

In collaboration with Dr. E. L. Compere[13] we have studied the conditions in rickets by means of direct observation and of calculation of Ca^{++} concentrations, with the result that no deviations from the normal were found. Scattered observations in certain other disorders of ossification, previously unpublished, are included in Table 2. The deviations between observed and calculated values for Ca^{++} in these observations are within the limits of error of the two methods. It follows from these observations, and from numerous observations in the literature upon diffusible and non-diffusible calcium, that the pathologic physiology of these disorders cannot rest upon any gross changes in the amount or state of calcium in

the blood stream. It also follows that, insofar as is now known, the finding of a normal total calcium level, associated with a normal protein level, means *ipso facto*, a normal Ca^{++} concentration, even in the presence of a known disorder of calcification or ossification. While these findings are in a sense negative, they may at least serve to limit speculation.

In the course of our studies it became almost immediately apparent that all gross changes in the calcium level in the plasma or serum fall into one of two categories. Since of these one is without direct clinical significance, and one is of serious clinical import, their differentiation, which depends upon the Ca^{++} concentration, obviously assumes importance.

Some years ago Salvesen and Linder[14] found, in cases of Bright's disease, that patients with hypoproteinemia showed also low total calcium values in the serum. Since then their findings have been abundantly confirmed, and in addition it has been found that patients with hyperproteinemia, the extreme of which is seen in cases of multiple myeloma, show high total calcium values. In both cases, the diffusible calcium has in general been found to be within normal limits.[15] It has been seen (Fig. 2) that if Ca^{++} concentrations are to remain within the normal range total calcium must rise and fall with changes in total protein, and that such a change in the calcium level must be regarded as a normal physiologic response. Clinical estimation of Ca^{++} concentrations, in these conditions, then become important as a means of ruling out disorders of calcium behavior, and will prevent needless attention being directed to findings which might otherwise be considered to represent pathologic variations in the behavior of calcium *per se*.

On the other hand, changes in the calcium level of the serum, associated with disorders of the regulatory mechanism, and consequently resulting in changes in Ca^{++} concentration, are invariably of serious import and deserve careful observation and consideration. Of these the most important are associated with disorders of the parathyroid glands, resulting on the one hand in the clinical picture of hyperparathyroidism and on the other hand in the picture of hypoparathyroidism and parathyroid tetany.

The authors, in collaboration with B. O. Barnes[16] have studied the influence of thyroparathyroidectomy and of the administration of parathyroid extract upon the calcium in the serum and have found no evidence of any qualitative change in its state, the changes observed being simply the quantitative changes predicted by the mass-law equation. As total calcium in the serum falls, following thyroparathyroidectomy, Ca^{++} falls in proportion. Conversely, as total calcium rises, following administration of parathyroid extract, Ca^{++} rises. While these observations have been made in largest number upon the cat and the dog, a number of observations have also been made upon man, in coöperation with Dr. W. O. Thompson,

and indicate that the findings from the animals used are also applicable in the clinic.

We have never observed parathyroid tetany at a Ca^{++} concentration above 3 mg. per 100 cc., corresponding, at 7% protein, to approximately 7 mg. total calcium per 100 cc. In acute hypoparathyroidism, as the Ca^{++} concentration falls below this level, the incidence of tetany increases, the most severe symptoms having been seen at a Ca^{++} concentration of 1.6 mg. per 100 cc. with total calcium 4 mg. Relief of the symptoms, following administration of calcium or of parathyroid extract, may occur with only a slight rise in the Ca^{++} concentration. In chronic hypoparathyroidism it appears that some adjustment is made by which animals remain symptom-free at Ca^{++} levels ordinarily associated, in the acute stage, with tetany. The tetany of alkalosis does not appear to be associated with diminished concentrations of Ca^{++} in the plasma.

We have not had the opportunity of studying spontaneous hyperparathyroidism.* Following the administration of parathyroid extract to man and to experimental animals the Ca^{++} level may rise to 6 to 8 mg. per 100 cc. In animals, death with the typical picture of hyperparathyroidism has been observed at Ca^{++} levels of 7 to 8 mg. with total calcium from 15 to 17 mg.

It would appear that the regulatory mechanism which maintains a relatively constant concentration of total calcium in the plasma, and with which the parathyroid glands are concerned, is in reality directed toward the maintenance of physiologic concentrations of Ca^{++} in the plasma. This conforms with the opinion stated in 1926 by Collip,[1] who wrote: "It is the opinion of this writer that the absolute concentration of calcium ions is the most important factor in calcium metabolism and that this factor is normally regulated either directly or indirectly by the parathyroid glands."

Prompt regulation of the Ca^{++} concentration in the plasma appears to be accomplished by control of a constant interchange between calcium in the dissolved form in the plasma and in the solid form in bone. Over longer periods of time regulation must depend eventually upon control of absorption and excretion. It should be emphasized that regardless of how or why calcium enters or leaves the blood, the Ca^{++} concentration in the plasma at any one time is determined almost exclusively by the concentrations of total calcium and total protein. While the organism as a whole acts, through the parathyroid glands, to maintain relatively constant Ca^{++} concentrations in the plasma, and does so by adding calcium to or removing it from the plasma, the distribution of this calcium, once in the blood, is wholly a physical-chemical matter.

* Since the above was written a diagnosis of hyperparathyroidism, confirmed by operation, has been aided by the following observations on the serum: total protein, 7.4%; total calcium, 16.6 mg. per 100 cc.; Ca^{++} calculated (Fig. 2), 7.5 mg. per 100 cc.; Ca^{++} observed, 7.1 mg. per 100 cc.

A close analogy with the regulation of hydrogen-ion concentrations in the blood may be drawn. The organism is relatively indifferent to the total amounts of acid and alkali in the blood, but is extremely sensitive to the hydrogen-ion concentration, which is the resultant of the balance between acid and alkali. Likewise the organism is indifferent to the total amount of calcium in the blood, but is sensitive to the Ca^{++} concentration, which is a resultant of the balance between calcium and protein. In both cases the immediate concentration of the physiologically active ion depends wholly upon the physical-chemical condition present in the blood at any one time, the organism as a whole functioning to maintain such conditions as will yield favorable concentrations of the ions. In both cases mechanisms exist for prompt regulation, in addition to regulatory processes involving longer periods of time. The calcium bound to protein insofar as it is of physiologic significance may be thought of as a reserve supply of easily available calcium, protecting the organism against too sudden changes in Ca^{++} concentration, and consequently analogous with the so-called alkalin reserve of the blood.

The finding of an abnormally high Ca^{++} concentration in the serum or plasma is presumptive evidence of hyperfunction of the parathyroid glands. So far as we now know, and except for the temporary hypercalcemia following intravenous administration of large doses of calcium, pathologic increases in Ca^{++} concentrations are caused only by hyperfunction of the parathyroid glands, overdosage with the parathyroid hormone and overdosage with viosterol. The latter condition we have not investigated.

On the other hand, the finding of an abnormally low Ca^{++} concentration presumably points to hypofunction of the parathyroid glands. A possible exception to this is the so-called low calcium rickets, associated with infantile tetany. The pathogenesis of this condition is not fully understood, but there is some reason to believe that the parathyroid glands are implicated and that, consequently, the general rule holds here also.

An exception to this rule, however, does exist in the case of uremia associated with hyperphosphatemia. In 1929, Peters and Eiserson[17] showed that the total calcium of the serum could, by means of an empirical equation, be correlated not only with protein, but also with phosphate, high phosphate being associated with low calcium. Since then, since it has been shown[18] that injection of phosphates into animals leads to the formation, in the plasma, of a colloidal complex of calcium and phosphate, it has seemed reasonable to suppose that part of the already low calcium, in cases of uremia with high phosphates, is in combination with the phosphates.

These relationships are being studied at the present time, experimentally in collaboration with Dr. Marie Hinrichs, and clinically in coöperation with Dr. Louis Leiter, and as a result of these un-

published studies it is possible to say that while we have confirmed the formation of a bound form of calcium in the blood, following intravenous injection of phosphates, this substance is quickly removed from the circulating blood of the animal, and that no evidence of its presence in the blood of uremic patients has been found. Consequently the calcium found in the serum of uremics, as in the case of the normal, is all accounted for as Ca^{++} and calcium bound to protein, and values for Ca^{++} calculated from the calcium-protein relationship are found to be valid.

The calcium-phosphate complex is apparently formed in the blood of these patients and is removed from the blood as rapidly as it is formed. This removal, however, is at the expense of the Ca^{++} concentration, and in nearly all cases of uremia low Ca^{++} values, as obtained by both methods, have been found. In some cases the findings characteristic of tetany have appeared and have been relieved by the administration of calcium. It would appear that tetany associated with low Ca^{++} concentrations in the plasma is not an unusual complication of uremia. Since in these cases the plasma proteins are often low, the finding of a low total calcium is not in itself necessarily diagnostic. Estimation of Ca^{++} concentration, however, will indicate the degree to which the calcium findings are to be regarded as pathologic.

TABLE 3.—CALCIUM IONS IN PLASMA OR SERUM.

Elevated (5.5 to 8 mg. per 100 cc.).	
	Hyperparathyroidism.
	Overdosage of viosterol.
Within or near the normal range (4.25 to 5.25 mg. per 100 cc.).	
	All conditions so far observed, except those listed above and below.
Lowered (1.5 to 4 mg. per 100 cc.).	
	Hypoparathyroidism, including parathyroid tetany.
	Hyperphosphatemia of nephritis and uremia.

The clinical findings with respect to Ca^{++} concentrations in the serum or plasma are summarized in Table 3. It will be seen that the essential change introduced by consideration of Ca^{++} rather than total calcium concentrations (Table 1) is that changes in the latter, occurring in response to changes in the concentration of protein, are no longer considered as in themselves abnormal. True abnormalities in the amount or state of calcium in the serum are limited to a small number of easily differentiated conditions and are more sharply related than heretofore to malfunction of the parathyroid glands.

Summary. 1. The total calcium of the serum or plasma is nearly all accounted for as calcium ions and calcium bound to protein. Of these two forms the ionized calcium is of primary physiologic and clinical importance.

2. The calcium-ion concentration of the plasma is normally maintained within a relatively narrow range by a process of physio-

logical regulation in which the parathyroid glands play a prominent part. This range has been found, as a rule, to be from 4.25 to 5.25 mg. per 100 cc.

3. The calcium-ion concentration of the plasma, at any one time, is the resultant of an equilibrium between the total calcium and total protein present in the plasma.

4. A method for clinical estimation of calcium-ion concentrations, by calculation from total protein and total calcium concentrations, is presented. Results obtained by this method have been found to be in substantial agreement with the results obtained by direct observation.

5. Fluctuations in the concentration of total calcium, occurring in response to fluctuations in the concentration of total protein in the plasma, are necessary for the maintenance of normal calcium-ion concentrations, and consequently are not in themselves of clinical importance.

6. An increase in the calcium-ion concentration in the plasma is presumptive evidence of hyperfunction of the parathyroid glands.

7. A decrease in the calcium-ion concentration in the plasma may occur as the result of hypofunction of the parathyroid glands, or may be brought about by the hyperphosphatemia of uremia.

8. In all other conditions investigated, including various disorders of calcification, the calcium-ion concentration of the serum or plasma has been found to be within normal limits.

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FAILURE TO FIND PRESSOR AND ANTIDIURETIC SUBSTANCES IN PATIENTS WITH TOXEMIA OF PREGNANCY.

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In 1931 Anselmino and Hoffman[1] reported evidence of the presence of a blood pressure raising and antidiuretic substance in the blood of patients with eclampsia and "nephropathie." They define "nephropathics" as "those patients who have hypertension, edema, albuminuria, and so forth, but who differ from those with eclampsia by the normal galvanic nerve-muscle response and by the absence of convulsions. Apparently this corresponds to our preëclamptic toxemia. This substance they believed closely allied to pituitrin because of similar behavior chemically (both substances are destroyed by alkali and ultraviolet light, and adsorbed on talcum) and because of the ability of the pituitrin to reproduce some of the features of eclampsia, such as convulsions and coma, increased blood pressure, hemoglobinuria and capillary spasm.

They used rabbits in their experiments. After having 90 cc. of water put into their stomachs with a stomach tube, these rabbits were injected subcutaneously with protein-free ultrafiltrates of serum from eclamptics and "nephropathics." A definite and marked inhibition of the normal diuretic response was noted. In other rabbits they observed a rise in the blood pressure of the carotid artery after injections of the ultrafiltrate from those patients with blood pressures over 180 mm. of mercury.

These findings seemed of the utmost importance in relation to the etiology and treatment of eclampsia and an attempt was made to repeat this work.

Methods. The methods described by Anselmino and Hoffman were followed, except those for the preparation of the collodion membranes with which to make the ultrafiltration and for the recording of the blood pressure. As many factors affect the permeability of collodion membranes, and we could not be certain of reproducing their membranes from the data given, a graded series of carefully standardized membranes was made with the technique of Dr. Edward Cohn.[2] As their purpose in filtering was simply to remove the serum proteins, a sac was used, the permeability of which was just sufficient to hold back the proteins. This was made with 3% collodion (made from dried DuPont's nitrocellulose, viscosity 43 seconds) in 25% anhydrous ether and 75% absolute alcohol. The glass mold was rotated 8 times a minute with an electric motor and the collodion applied at an even rate from a separating funnel. Four reënforcing coats were applied at top and bottom at 5-minute intervals and then 4 filtering coats at 3-minute intervals. Ten minutes after the last coat, the sac was placed in 95% alcohol for 30 minutes and then in distilled water until used. A new sac was used for each serum. It was mounted in a suction apparatus made by MacAlaster-Bicknell of Cambridge and filtration carried out at a negative pressure of 150 mm. of mercury. This was obtained with a water pump and a mercury valve. After the preliminary work the graded series was obtained by varying only the time between coats. The series was checked at intervals to be sure that the sac used gave the desired permeability. The sac used, as well as a much less permeable membrane in the series, was shown to allow easy passage of pituitrin mixed with acidified plasma.

To determine the blood pressure effects rabbits were lightly anesthetized with ether, an incision made in the neck and a section of the carotid artery brought outside of the skin. At least 6 hours were allowed for recovery and a new rabbit was used for each experiment. At the time of the experiment the carotid artery was cannulated under local cocain anesthesia and the blood pressure recorded on a kymograph with a mercury manometer. A control record of 30 minutes to an hour was taken to show the normal variations and the effect of slight manipulation of the animal. Thus a continuous written record was obtained which was thought to be more reliable than any type of intermittent reading of pressure.

One hundred cubic centimeters of blood were obtained from the patient and 5 cc. of 5% sodium citrate were added; 50 cc. of plasma were removed and acidified by the addition of 2.5 cc. 1 N. acetic acid. It was then put into the collodion sac and suction started. The ultrafiltrate was always clear, colorless and albumin-free by biuret and nitric acid tests. In some instances it was stored in the icebox overnight. Immediately before using, it was neutralized with 1 N. sodium hydroxid to pH 7, using a spot plate and bromthymol blue as an indicator.

For the antidiuretic experiments only rabbits were used which had relatively consistent diuresis curves after receiving 90 cc. of water by stomach tube and 10 cc. of saline subcutaneously. They were kept without food or water from 12 to 15 hours before the experiment. Over half of the rabbits had to be discarded because of inconsistent diuresis curves, and of the remainder 3 well controlled rabbits were used for the majority of the experiments. There was some variation in the height of the diuresis even in these rabbits, but there was always a striking difference after the injection of small amounts of pituitrin or pitressin. The results obtained with one of these rabbits are shown in Table 1. Of the ultrafiltrate, 10 cc. were

injected subcutaneously in the experiments, while the controls were given 10 cc. of saline. All saline given subcutaneously was 0.85% sodium chlorid which had been neutralized with 1 N. sodium hydroxid after the addition of 5 cc. of 1 N. acetic acid per 100 cc. of saline.

Case Abstracts. *Patients with Toxemia.* Case 1.—Mrs. M. B., aged 34, Para VI. Previous deliveries normal. Well during this pregnancy until 3 weeks ago when feet and hands began to swell. No other symptoms.

Physical examination negative except for slight pitting edema of lower legs. Eight months pregnant. Blood pressure, 194/100. Albumin—large trace with numerous hyalin and granular casts. N. P. N., 25. Patient was kept for 2 weeks during which time blood pressure was 140/90–100. Urine showed large trace of albumin. Membranes ruptured 2 weeks after entry and patient had a normal delivery of a normal baby. Just before delivery blood pressure was 160/110. Patient had a normal convalescence with the blood pressure going down to 110/80 and a very slight trace of albumin with no casts. Blood taken 2 days after entry when blood pressure was 194/120.

Diagnosis. Preëclamptic toxemia.

Experimental Observations. No antidiuretic response. No pressor response.

Case 2.—Mrs. K. M., aged 36, primipara, due April 4, 1933. Sent in March 25, 1933, by local physician because of increased blood pressure and albuminuria for 1 week. Patient had felt entirely well until March 15 when feet and hands became swollen. Blood pressure on entry was 196/130 and urine showed a trace of albumin. *Past history* negative. Blood pressure normal in early pregnancy. *Physical examination:* Obese, hirsute woman with marked edema of both legs, moderate edema of hands, face and sacrum. A few râles noted at both bases. Blood pressure varied between 170–190/100–110 for the first 4 days. Blood was taken on third day for pressor and antidiuretic effect. On the fourth day a baby, 8 pounds, 11 ounces, was delivered by Cesarean section. Urine showed a large trace of albumin on entry. After section blood pressure gradually came down to 130 and the albumin decreased. When seen 6 months later blood pressure was 120/72. No albumin present. Patient felt perfectly well.

Diagnosis. Preëclamptic toxemia.

Experimental Observations. No pressor effect.

Case 3. Mrs. C. C., aged 38, old primipara due February 17 and sent in February 1, 1933, because of high blood pressure and albuminuria.

For the past 3 months patient had had increasing edema of the ankles, headache for 1 month, vomiting off and on for 1 month, and blurred vision of the right eye for 1 week.

On entry, patient had marked edema of the hands and slight edema of face. Blood pressure was 220/164. Albumin—trace to large trace with many hyalin casts and a few granular casts. For 2 days blood pressure remained 210/98–120 and then a classical Cesarean section was done under spinal anesthesia. Blood for determination of pressor and antidiuretic substance was taken on day of operation. After operation the blood pressure gradually came down to 130/88 and the urine showed a slight possible trace of albumin. The baby did well. Since delivery, patient has shown no albumin and the blood pressure has been 126–134/84.

Diagnosis. Preëclamptic toxemia.

Experimental Observations. No antidiuretic response. No pressor response.

Case 4.—Mrs. G. A., aged 27, Para IV, due August, 1933, was referred on June 26 from district for swelling of hands, face and feet, and hypertension. Blood pressure, 184/108, and large trace of albumin. Blood pressure continued at 190/100 and albumin showed a trace for 10 days

when she went into labor and delivered normally a stillborn infant. After delivery blood pressure fell to 120/80 and albumin disappeared. Blood was taken the day after entry.

Diagnosis. Preëclamptic toxemia.

Experimental Observations. No antidiuretic response. No pressor response.

CASE 5.—Mrs. A. F., aged 32, Para IV, due May 27, 1933. Patient entered May 28, 1933, because of acute pulmonary edema. On admission was markedly dyspneic; blood pressure was 195/100; pulse, 120. She had a presystolic murmur. Lungs were full of râles. Patient given morphin during the night. Blood taken for pressor antidiuretic response that night. The next day patient went into labor and delivered a normal infant. After delivery blood pressure went down gradually to 150/100, where it remained for a week then went down to 120/70. Urine showed a trace of albumin on entry and for first few days. Since discharge patient has had no albumin, no elevation of blood pressure and no dyspnea.

Diagnosis. Preëclamptic toxemia, rheumatic heart disease, mitral stenosis.

Experimental Observations. No pressor effect.

CASE 6.—Mrs. V. G., aged 41, para VII, due May, 1933. Referred on May 27, 1933, with blurred vision, headaches of 2 months' duration, edema of legs for 2 months. Blood pressure was 190/120 and eyegrounds showed many large and small areas of cotton-wool exudate and many small hemorrhages in the retina. Blood pressure remained 180–190/120. Membranes were ruptured on May 29 and patient went into labor and delivered a stillborn infant full of congenital abnormalities. Placenta was normal. After delivery, blood pressure was 170/110; albumin, negative; fundi unchanged. When seen 6 weeks later blood pressure was 160/96; albumin, negative.

Diagnosis. Toxemia, superimposed upon underlying hypertension.

Experimental Observations. No pressor effect.

CASE 7.—Mrs. C. C., aged 22, primipara, due April 10, 1933. Patient sent in February 25, 1933 because of edema of ankles, headaches, of 1 week's duration. On entry blood pressure was 160/98; albumin, trace; marked edema of legs. On February 28, 1933, blood taken for pressor-antidiuretic test. Blood pressure was 164/94 at that time. Albumin and hypertension continued 1 week, then gradually decreased. On March 7 patient discharged with normal blood pressure and no albumin. Seen again March 31. Blood pressure was 150/100 and a large trace of albumin was present. On April 2 patient entered in active labor, delivered normally of a baby, 6 pounds, 6 ounces. Blood pressure and albumin decreased to normal after delivery.

Diagnosis. Preëclamptic toxemia.

Experimental Observations. No antidiuretic response. No pressor effect.

CASE 8.—Mrs. A. C., aged 36, old primipara, entered the hospital on May 17, 1933, 2 weeks from term, with a history of a convulsion 2½ hours before admission, vomiting, incoördinated movements and coma. Apparently perfectly well until 9 A.M. of day of admission when she complained of nausea, vomiting and epigastric pain. At 5 P.M. patient had a convulsion and was brought into the hospital.

On entry, patient was found to be an obese Italian woman, semicomatose, vomiting dark yellowish material. Incoördinated movements continued. Edema of ankles present. Blood pressure 124/80. Eye grounds showed fair sized nerve fiber layer hemorrhage below left disk, retinal veins distended and moderate retinal sclerosis. Urine showed large trace of albumin, and was loaded with red and white blood cells and casts. N. P. N., 35. Blood pressure varied between 130–180/90–100 for first 2 to 3 days after admission. Membranes then ruptured and an edematous stillborn was

delivered. Patient constantly improved after delivery and on postpartum visit had a normal blood pressure. No albumin present. Blood was taken on night of admission.

Diagnosis. Eclampsia.

Experimental Observations. No antidiuretic response.

Patients With Antecedent Hypertension, Vascular Changes, Chronic Nephritis.

CASE 9.—Mrs. G. N., aged 43, Para III, sent in at term because of hypertension.

Past history negative. Patient felt entirely well during this pregnancy. Had edema of both ankles for 4 months, swelling of hands for 2 or 3 months, face for 1 month. Patient did not go to a doctor until just before entry when blood pressure was found elevated and she was sent into the hospital.

On entry, legs were markedly edematous, also sacrum. Fingers and face moderately swollen. Two and a half days after entry 100 cc. of blood taken. Blood pressure, 200/126. Urine showed a large trace of albumin with many hyalin and fine granular casts. Patient went into labor soon after and had a normal delivery of a healthy baby. Since delivery patient has continued with her hypertension but has had no albumin and has had signs and symptoms of mild heart failure.

Diagnosis. Vascular hypertension.

Experimental Observations. No antidiuretic response. No pressor effect.

CASE 10.—Mrs. G. M., aged 32, Para V, due March 26. Entered hospital March 8, sent in because of hypertension. Blood pressure, 195/115 and urine showed trace of albumin.

On entry, patient had fluid at both bases. With rest in bed patient lost weight but blood pressure remained at 170/120 and she continued to show a trace of albumin. Three days after entry patient delivered a stillborn baby. N. P. N., 40. Blood for analysis taken on day after admission, on which day blood pressure had been 180/120. After delivery, patient had 2 attacks of nocturnal dyspnea and was transferred to another hospital for treatment. Blood pressure continued elevated 150/100 during remainder of hospitalization.

Diagnosis. Vascular hypertension plus cardiac decompensation (possible superimposed toxemia).

Experimental Observations. No antidiuretic response. No pressor effect.

CASE 11.—Mrs. O. D., aged 33, Para VII, due May 29. Patient sent in March 22, 1933, because of hypertension on her first visit. Obstetric history negative until 1927 when she had high blood pressure at end of fourth pregnancy. In 1929 had elevated blood pressure with fifth pregnancy but no albumin. In 1932 patient had a macerated fetus. Blood pressure readings not obtained after deliveries. She had felt perfectly well this pregnancy. Blood pressure, 230/130. Albumin, none. Patient had no edema. Uterus was the size of a 5 months' pregnancy. Eyegrounds showed slight to moderate sclerosis of retinal arteries. On March 27 patient went into labor and delivered a 6¾ months' macerated fetus. After delivery, blood pressure remained at 200/90–130. Urine negative for albumin. Patient has not been seen since discharge.

Diagnosis. Vascular hypertension.

Experimental Observations. No antidiuretic response. No pressor effect.

Non-pregnant Hypertensives.

CASE 12.—Mrs. A. C., aged 43, Para V, entered the hospital on July 30, 1932, when 2 months pregnant with a blood pressure of 240/136. Urine showed no albumin. Patient had an elevated blood pressure since her second pregnancy 10 years ago. Patient complained of headache and spots

before the eyes of 1 month's duration, also of increased drowsiness and irritability for 4 to 6 weeks. Physical examination negative except for sclerosis of retinal arteries. Very slight trace of albumin. N. P. N., 48. On August 8 a hysterectomy was performed. Following operation blood pressure was 180–210/120–140. In the postpartum clinic blood pressure was 208/140, 230/150. On March 13, 1933, 6 months after operation, patient had a urea clearance test, at which time blood was taken to test for pressor antidiuretic effect. Blood pressure at this time, 230/150. Urea clearance test was normal (108%).

Diagnosis. Non-pregnant hypertensive.

Experimental Observations. No antidiuretic response. No pressor effect.

CASE 13.—Mr. S. K., aged 57, entered the hospital March 8, 1933, because of pains in the legs for 2 months. He had had hypertension for several years. His heart was enlarged to the left. Blood pressure was 245/130. Urine, negative. Blood taken for pressor-antidiuretic test on March 10, 1933.

Diagnosis. Hypertension, chronic myocarditis, arteriosclerosis.

Experimental Observations. No pressor effect. No antidiuretic response.

CASE 14.—Mr. H. L., aged 56, janitor, entered the hospital because of nocturia, headache, blurring of vision, of 15 years' duration. Patient had marked thickening of peripheral arteries. Blood pressure, 230/130. Eyegrounds showed both nerves markedly blurred in outline. Several hemorrhages and considerable exudate in both retinæ. Heart enlarged transversely. Blood pressure over 220 during hospital admission.

Diagnosis. Hypertension, arteriosclerosis, chronic myocarditis.

Experimental Observations. No pressor effect.

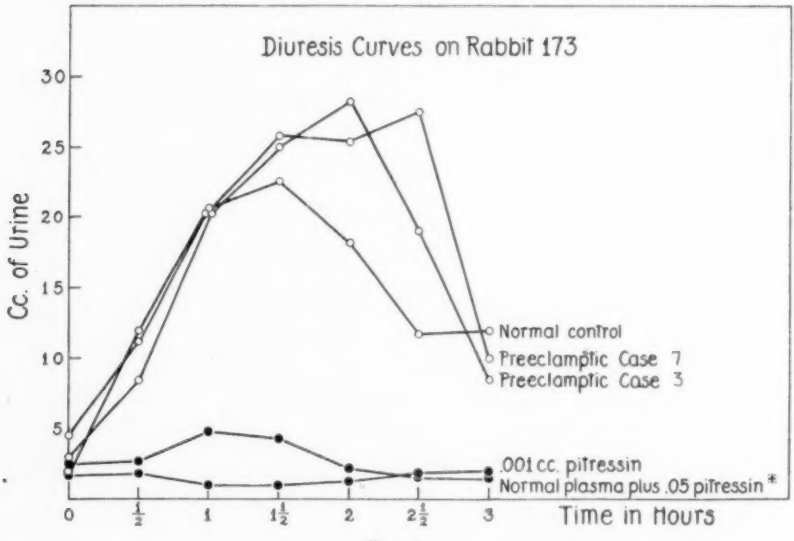

FIG. 1

Results. Blood was obtained from 1 eclamptic, 7 preëclamptics, 3 pregnant women with hypertension and chronic nephritis, and 3 non-pregnant patients with hypertension.

Antidiuresis. Figure 1 gives the diuresis curves in the rabbit (No. 173) after receiving 90 cc. of water by stomach tube in each

instance and 10 cc. subcutaneously of saline, pitressin in saline, ultrafiltrate of normal acidified plasma plus pitressin, or ultrafiltrate from blood of patient with toxemia. None of the ultrafiltrates caused any inhibition of diuresis while 0.001 cc. of pitressin was adequate to cause a definite and lasting antidiuresis. Similar results were obtained with the other filtrates. Nor could a consistent change in the sodium chlorid concentration be demonstrated.

TABLE 1.—DIURESIS CURVES ON ONE RABBIT, NO. 173 (CC. OF URINE).

Date	Control, ½ hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	2½ hrs.	3 hrs.	Injected 10 cc. of
12/6/32	0.0	7.7	6.2	14.8	10.8	10.8	12.0	Saline.
12/8	2.3	5.6	13.5	14.9	18.0	16.8	11.0	Saline.
12/10	2.0	12.0	20.6	22.5	18.2	11.7	12.0	Saline.
12/12	2.0	2.7	2.8	2.0	1.0	0.8	1.6	0.01 Pitressin.
12/14	2.4	6.0	16.3	21.2	18.6	18.8	19.2	Saline.
12/16	1.8	1.8	0.9	1.0	1.3	1.9	2.0	0.001 Pitressin.
12/24	3.0	1.8	13.5	20.2	22.0	9.1	....	Saline.
1/3/33	1.0	3.0	7.8	13.9	12.8	17.0	13.2	Saline.
1/23	2.0	6.0	13.0	20.0	11.8	13.4	....	Saline.
2/4	2.5	2.7	4.8	9.5	14.0	17.6	17.4	Case 8.
2/14	2.6	1.7	1.8	4.4	2.2	1.6	1.6	0.01 Pitressin.
2/15	2.0	2.6	6.3	13.3	32.2	30.4	24.2	Saline.
3/1	3.0	8.5	20.8	25.8	25.4	27.5	10.0	Case 7.
3/3	1.0	1.0	10.0	25.0	30.0	23.5	11.5	Saline.
3/7	1.8	11.2	20.5	25.0	28.2	19.0	8.5	Case 3.
3/11	2.5	2.5	12.4	22.0	17.5	22.4	13.0	Case 2.
3/16	2.1	....	30.0	28.2	36.7	16.5	8.0	Case 9.
3/21	1.5	1.8	12.2	22.7	18.7	9.2	....	Case 11
4/23	2.2	1.0	14.4	25.0	20.5	18.5	....	Case 10
4/25	3.0	6.0	30.0	26.0	32.0	28.0	23.5	Saline.
5/18	2.0	10.5	27.0	34.0	32.0	9.0	3.5	Case 12
6/28	1.5	17.5	21.7	29.0	26.3	24.5	13.8	Case 4.
7/6	2.4	0.0	5.2	14.6	22.4	15.0	12.0	Case 1.

Pressor Effect. No pressor response was observed after the injection of any of the ultrafiltrates, while small doses of pitressin (0.01 cc.) intravenously caused a slight rise in blood pressure and then a fall followed by a return to normal. Larger doses of pitressin (0.02 cc.) caused a more marked fall after the slight rise. Even after prolonged observation of the blood pressure there was no rise at all after the injection of the ultrafiltrates either subcutaneously or intravenously.

Conclusions. Neither blood pressure raising nor antidiuretic substances were found in the blood of 14 patients classified as non-pregnant hypertensive (chronic nephritic) toxemia, preëclamptic toxemia, and eclampsia.

NOTE.—Since this paper was written an article has appeared by Byrom and Wilson (Quart. J. Med., **3**, 361, 1934) also failing to find antidiuretic substances in the blood of patients with preëclamptic toxemia and eclampsia.

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THE HISTOPATHOLOGY OF THE HEMOPOIETIC TISSUES IN HEMOPHILIA.

AN UNEXPLORED FIELD.*

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Necropsies on cases of hemophilia have been strangely infrequent in recent times, and of those in the literature concern has been chiefly with the hemorrhage found, the secondary degenerations and necroses and the condition of the vessel walls, rather than with the state of the hemopoietic tissues, an omission which seems particularly odd in view of the usual belief that the blood platelets are at fault in this disease. Since Neumann first connected the bone marrow with hemopoiesis (1868), we have not been able to find a single published necropsy on a case of hemophilia that has included a study of the hemopoietic tissues. The unusual circumstance, then, of having 3 cases of hemophilia come to necropsy within a short period, has led us to study the postmortem picture in the hope that further light might be thrown on the nature of the disease and in the belief that, in any case, published studies by modern methods would be of service. The 3 cases were the more valuable for the purpose in that, as seen below, one died as the direct result of hemorrhage, another of a combination of infection and hemorrhage and the third of infection without any relation to hemorrhage, thus constituting three variants of a natural experiment, the subjects being of approximately the same age.

Of particular interest was the bone marrow cytology, which is therefore presented in detail, especially that of the megakaryocytes, which are generally regarded as the originators of the blood platelets and directly concerned with blood coagulation, the major disturbance in hemophilia.

Abstracts of the clinical and postmortem findings follow:

Case Abstracts. Case 1.—An Italian boy (F. P.), aged 11, was admitted to the Philadelphia General Hospital February 5, 1935 (service of Dr. Eliason; attending, Dr. Ferguson), having fallen on January 30, 1935. He complained of pain in back on February 2, limped with the right leg and

* This is regarded as No. V in the series of "Studies on the Structure and Function of Bone Marrow," this general title being subordinated that the main subject might not be overlooked.

ultimately was confined to bed with intense abdominal pain in lower right quadrant. He vomited twice on February 3. *Past History:* First hemophilic tendency appeared at 7 months, with prolonged hemorrhage following incision of gums to aid teething. Minor lacerations bled for days, requiring hospitalization on many occasions. He had had several "rheumatic attacks" and, on previous admission, murmurs were heard over mitral and tricuspid areas. *Family History:* Possibly the first generation of hemophilia (little information available concerning relatives in Italy); a brother, aged 7, shows bleeding time of 2 minutes and coagulation time of 24 minutes; a nephew, age 20 months, shows bleeding time of 2 minutes and coagulation time of 15 minutes, each having shown hemophilic signs and symptoms since infancy. A control test on a healthy person gave a bleeding time 1 minute and coagulation time 4 minutes. *Physical Examination:* Acutely ill child in severe pain, with right thigh flexed on abdomen; head and neck normal except for coryza and tonsillar hypertrophy; lungs present vague impairment at right apex, friction rub at right base, fine basal and interscapular râles; heart normal except for tachycardia; right lower quadrant of abdomen extremely tender and rigid with a palpable mass (hemorrhagic? inflammatory?); marked rectal tenderness; extremities normal except for abnormal flexion of right leg (enlarged knee joints on previous admission). *Laboratory Tests:* Urine shows trace of albumin and occasional leukocytes; erythrocytes 4,120,000 to 4,130,000; leukocytes 17,150 to 20,800; neutrophils 72% (myelocytes, 0; juv., 0; stab, 40; segmented, 32), lymphocytes 26%, monocytes 2%; coagulation time, 35 minutes; bleeding time, 3 minutes; electrocardiogram, normal; tuberculin test doubtfully positive. *Course:* February 5, 1935, exploratory laparotomy showed extensive retroperitoneal hemorrhage; no intraperitoneal lesion found (Bovie knife used and no operative hemorrhage incurred). February 6, abdomen tense and tender; rising temperature, pulse and respiration; February 7, death. *Final diagnosis:* Hemophilia with massive extraperitoneal hemorrhage.

Necropsy (P. G. H., 28846, 7 hours after death, Dr. R. W. Mathews). Well-developed male, height 132 cm., weight 24.5 kg., with recent surgical incision in right lower abdominal quadrant; no external evidence of hemorrhage. On opening abdomen an extraperitoneal hematoma is encountered of 2 to 4 cm. thickness, covering entire right lower quadrant, the medial half of left lower quadrant and laterally over entire right flank, extending from diaphragm over right psoas along the intermuscular fascial planes well into right thigh. There is intrapsoas hemorrhage with muscular necrosis. *Aorta* is smooth, elastic and of normal caliber. *Heart* weighs 140 gm. (left ventricle, 1.3 cm.; right ventricle, .4 cm.; aortic valve, 4.5 cm.; mitral, 8 cm.; tricuspid, 9 cm.; pulmonary, 5.5 cm.), being slightly enlarged; pericardium at apex thick, gray and shaggy; myocardium firm and pale red-gray; auricular endocardium slightly thickened; aortic leaflets uniformly thickened but functionally competent; free edges of mitral leaflets thickened and rolled and chordæ tendineæ shortened and thickened, papillary muscles being hypertrophied and shortened; coronary vessels apparently normal. *Lungs* present glistening pink-gray pleuræ, left weighing 140 gm., right 180; parenchyma soft, tough and inelastic; crepitant throughout; tracheobronchial tree congested and contains blood-tinged mucoid exudate. *Spleen* weighs 80 gm. and measures 9 by 6.5 by 3 cm., capsule being smooth, gray and glistening; parenchyma gray-red, firm and resilient, follicles visible as gray dots. *Lymph nodes* appear normal. *Kidneys* show variation in size, left weighing 60 gm. and measuring 7 by 4 by 2 cm.; right 100 gm., 11.5 by 4 by 3 cm.; each being of normal shape; capsules thin, strip with ease leaving smooth, pale brown surfaces; cut edge slightly rolled and blood oozes from cut surface; general architecture normal. Lower urinary tract and genitalia show no lesions. *Gastro-intestinal tract* including appendix

appears quite normal. *Liver* weighs 800 gm. and measures 15 by 8.5 by 5 cm., presenting a thin capsule and fairly firm red-brown parenchyma that retains normal lobular architecture; blood oozes from cut surface; gall bladder and bile ducts appear normal. *Pancreas* firm, gray-pink and apparently normal. *Adrenals* show yellow cortices and dark brown medullæ. *Skeleton* appears normal, bone marrow being dark red (vertebra, sternum, rib and femur). HISTOLOGY. *Heart* shows slight subepicardial fibrosis with minor lymphocytic infiltration; myocardium slightly degenerated; mitral valve thickened and distorted, changes being characteristic of rheumatic residuum; coronary arteries normal save for slight intimal proliferation and rhexis of elastica in one of main branches. *Lungs* present moderate emphysema accompanied by thickening of many septa as result of endothelial proliferation and leukocytic infiltration (rheumatoid interstitial pneumonitis). *Spleen* retains normal architecture, Malpighian bodies being slightly smaller than usual, many containing no so-called germinal centers; an intrafollicular hyalin material, appearing sometimes as conglutinated erythrocytes, sometimes as collagenous transformation of the reticulum, noted; there is increase in cells of the reticulo-endothelial system, the sinus endothelium being hypertrophic; occasional megakaryocytes, usually with pyknotic nuclei, lie in sinuses; moderate arteriolar thickening and hyalinization present. *Lymph nodes* exhibit reticulo-endothelial hyperplasia, architecture being preserved. *Kidneys* show no lesions other than cloudy swelling of the convoluted tubular epithelium; an entrapped megakaryocyte is noted in a glomerular tuft. *Liver* architecture normal, the epithelium being swollen and granular; occasional hypertrophic Kupffer cells are seen; portal triads appear normal. *Pancreas* the seat of slight interlobular fat infiltration but otherwise quite normal. *Appendix* moderately fibrosed but shows no definite lesion. *Adrenals* present partial loss of cortical lipoid material; eosinophilic bodies at corticomedullary junction particularly prominent. *Bone marrow:* Sternum is about 90% cellular, about half the cells belonging to the erythropoietic series, with occasional megaloblastic foci; red blood cell formation is of the normoblastic type and most of the cells are observed in this late stage of differentiation. Granulopoiesis is also of normal type with complete intramedullary maturation of neutrophils; eosinophils are somewhat more abundant than usual. Megakaryocytes are particularly prominent, usually with abundant cytoplasm and more or less pyknotic nucleus; the cytoplasm of the more degenerate forms often contains one or more neutrophils and monocytes; megakaryoblasts are encountered frequently, either as hypertrophied mononucleated cells or in a state of beginning nuclear segmentation. In 4 instances megakaryocytes situated in immediate juxtaposition to blood sinuses are observed to present the so-called "Wright's figures," *i. e.*, cytoplasmic pseudopods extending through the sinus wall into the lumen (Plate I, *A* and *B*). Cells of the general reticulum are rather more prominent than usual and may be seen differentiating toward megakaryoblasts or myeloblasts, the latter particularly in the periphery of bone trabeculæ and sinus margins.

The vertebral marrow contains slightly more fat than the sternal, being about 80% cellular, and shows somewhat less erythropoiesis than in the sternum, a rather unusual circumstance; the incidence of megakaryocytes, however, is approximately the same. Rib marrow resembles the vertebra very closely.

CASE 2.—An Italian boy (C. C.), aged 13, was admitted to the Philadelphia General Hospital (service of Dr. Warmuth; attending, Dr. Wright) on December 26, 1934 with diagnosis of acute appendicitis. His illness began December 23, 1934 with severe upper abdominal pain followed by nausea, vomiting and pain shifting to right lower quadrant. *Past History:* Patient has "bruised easily" all his life and small cuts have often bled for a week;

extensive hemorrhage followed tooth extraction at 10; after violent exercise joints would swell and become painful, the knees being most frequently involved. *Family History:* Probably first generation of hemophilia (careful inquiry into maternal family history being quite negative); patient's mother and her sister have each borne hemophiliacs, the former 3, the latter 2; bleeding time of brother 1½ minutes, coagulation time, 9¾ minutes (control for method, 1 and 4 minutes respectively). *Physical Examination:* Well-developed adolescent showing normal head, neck, lungs and heart; abdomen extremely tender in right lower quadrant with suggestion of mass above anterior superior spine; peristalsis absent in this region but active elsewhere; rectal tenderness on right; both knee joints enlarged but not tender. *Laboratory Tests:* Urine shows trace of albumin, a few leukocytes and many granular casts; leukocytes 18,650 (neutrophils 88%, lymphocytes 6%, monocytes 5%, basophils 1%); plaetlets 260,000; coagulation time, 11½ to 14 minutes; bleeding time 1½ to 8 minutes (control as above); blood Type IV. *Course:* December 25, 1934, removal of ruptured gangrenous appendix and drainage of periappendiceal abscess; marked oozing of blood, especially from omentum; December 26, 1934, oozing continued; no response to theelin, thymus extract, thromboplastin or transfusion. December 27, 1934, bleeding continuously from drain; progynan had no effect. December 28, 1934, tympanites and vomiting; bleeding definitely lessened by thromboplastin injected into drainage tract. December 29, 1934, profuse vomiting followed by death.

Necropsy: (P. G. H., 28656, 5 hours after death, Dr. R. W. Mathews). Well-developed male, height 158 cm., weight 46.3 kg. with recent oblique surgical scar in right lower abdominal quadrant. Peritoneum covered by thin layer of soft, clotted blood; omentum drawn over intestines in right lower quadrant. All organs are pallid and on section ooze very little blood. *Aorta* of normal caliber and elasticity. *Heart* weighs 220 gm. (aortic valve, 5.5 cm.; mitral, 7.5 cm.; tricuspid, 10 cm.; pulmonary, 6 cm.); no anatomic lesions except for pallor of myocardium. *Lungs* are soft and crepitant, left weighing 280 gm., right 290 gm., blood-tinged frothy fluid being expressed from the cut surface. *Spleen* weighs 130 gm. and measures 12 by 7 by 3.5 cm. with thin capsule, soft, gray-red parenchyma in which follicles are visible. *Kidneys* weigh 150 gm. each, left measuring 11.5 by 4 by 3 cm.; right, 12 by 3 by 4 cm.; the thin capsules strip readily leaving smooth surfaces; cut edges slightly rounded and corticomedullary ratios normal. Lower urinary tract and genitalia are essentially normal. *Gastro-intestinal tract* is normal, except for terminal ileum and cecum which form the center of an inflammatory mass in right lower quadrant. This is well walled off from the general peritoneal cavity by the omentum and contains a small hematoma. The appendiceal and mesoappendiceal stumps are obviously the source of hemorrhage. *Liver* weighs 1340 gm. and presents a pale brown, soft parenchyma; *gall bladder*, *pancreas* and *adrenals* appear normal. *Skeleton* is apparently normal; bone marrow is pale pink.

Histology. *Heart* presents marked degenerative changes in the congested myocardium. *Lungs* are congested and edematous and the seat of bacterial colonization within septa, both coccal and bacillary. *Spleen* presents small follicles without germinal centers and hyperplasia of reticular and endothelial elements, fixed and wandering, in the pulp. A single megakaryocyte is noted in a sinus. *Lymph nodes* retain normal architecture, distorted through hyperplasia of cells of reticulo-endothelial system, the sinuses being filled with macrophages. *Kidneys* are normal save for cloudy swelling of convoluted tubules and venous engorgement. *Liver* epithelium is swollen and granular; Kupffer cells are prominent and seen occasionally in various stages of detachment. Cecum presents a thickened wall extensively infiltrated by macrophages, the mucosa covered by blood and fibrinopurulent exudate. *Adrenal* cortex has lost considerable lipoid, medullary cells being

degenerated and central vein recently thrombosed. *Bone marrow:* Sternum is approximately 70% cellular, the granulocyte series being slightly in excess of the erythrocyte progenitors; maturing forms of each group are structurally normal. Megakaryocytes are noted mostly in a degenerated state as judged by marked nuclear pyknosis, karyolysis, cytoplasmic vacuolization and fraying of cell margins; cells of this series are considerably in excess of the control group (Table 2). Vertebral marrow is somewhat more cellular and shows a predominance of cells of the granulocyte series. Megakaryocytes are more numerous than in sternal marrow and normal forms are seen as frequently as degenerated cells.

CASE 3.—A Jewish boy (M. U.), aged 13, was admitted to the Hospital of the University of Pennsylvania (service of Dr. Gittings) December 11, 1934. His illness began suddenly the day before with sore throat, headache, fever and productive cough; "prune juice" sputum, high fever and delirium on day of admission. *Past History:* No undue hemorrhage after circumcision, first sign of hemophilia being sublingual bleeding for 4 weeks without apparent

PLATE I.

(All sections from Case 1.)

A. Bone marrow (sternum)—young megakaryocyte on sinus margin with two Wright's figures (WF) projecting into sinusoid; adjacent cells are erythroblasts and normoblasts (× 598). In the sinus, whose lumen extends beyond the margin of the figure, the lower platelet projection is the longer and paler of the two. It is limited below by a darker staining, oblong erythrocyte. *B*. Bone marrow (vertebra)—another megakaryocyte on sinus margin showing a short, blunt Wright's figure (WF); degenerated megakaryocyte in lower left (× 598). *C*. Bone marrow (vertebra)—showing megakaryoblast, developing megakaryocyte and degenerate megakaryocyte, adjacent cells being chiefly erythroblasts (× 598). *D*. Bone marrow (rib)—essentially the same picture as *C* (× 598). *E*. Heart—coronary arterial wall above presents proliferative intimal thickening; myocardial fibers show slight degenerative changes (× 103). *F*. Lung—emphysema and interstitial pneumonitis (rheumatoid) (× 92). *G*. Spleen—margin of follicle showing several thickened and hyalinized arterioles; megakaryocyte seen in lower right (× 69). *H*. Lymph node with prominence of reticular and wandering cells (× 322). *I*. Kidney—glomeruli are normal and convoluted tubular epithelium shows cloudy swelling (× 92). *J*. Liver—cloudy swelling of epithelium; normal portal triad in upper right (× 103). *K*. Pancreas—normal artery with normal island to left; parenchyma shows no lesions (× 92). *L*. Adrenal—zona fasciculata in lower half, cells being poor in lipoid; zona reticularis crosses center and medulla lies above; wall of central vein in upper left (× 103).

PLATE II.

A. Bone and marrow (sternum—Case 3)—low power of cross section showing normal trabeculation and partially fatty marrow. *B*. Bone marrow (sternum—Case 3)—showing megakaryocyte adjacent to dense focus of erythropoiesis (× 598). *C*. Bone marrow (femur—Case 3)—showing predominance of granulopoiesis; degenerated megakaryocyte lies in midleft (× 598). *D*. Bone marrow (sternum—Case 2)—several degenerated megakaryocytes; about equal numbers of erythropoietic and granulopoietic cells compose the background (× 598). *E*. Bone marrow (vertebra—Case 2)—three megakaryocytes; other cells are predominantly erythroblasts (× 598).

KEY FOR ILLUSTRATIONS.

ERBL—erythroblast; ERC—erythrocyte; FC—fat cell; L—lymphocyte; MBL—myeloblast; MGBL—megaloblast; MKBL—megakaryoblast; MKC—megakaryocyte (normal); MKC-D—megakaryocyte (degenerated); MLC—myelocyte; MMLC—metamyelocyte; NBL—normoblast; PMLC—promyelocyte; R—reticulum cell; WF—Wright's figure.

Letters are placed when possible immediately below the cell indicated; a small addended "s" indicates a group of cells of the same type. All bone marrow sections stained by modification of Maximow's azure II-eosin; other viscera stained with hematoxylin-eosin; paraffin sections; photomicrographs, by Gosner and Sheppard, Phila. Gen. Hosp., with Leitz apochromatic optical system; Wratten and Wainwright M plates.

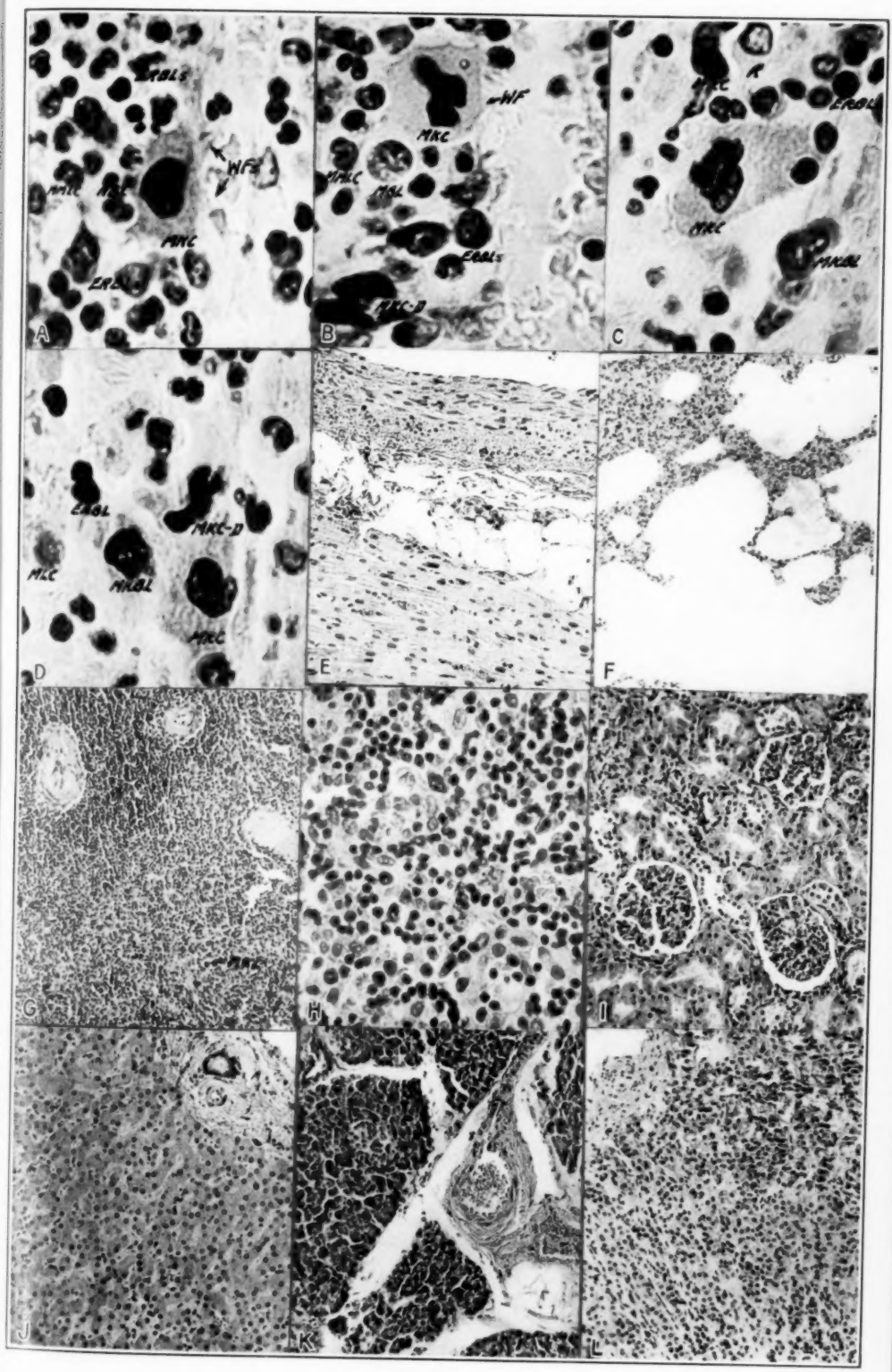

PLATE I.

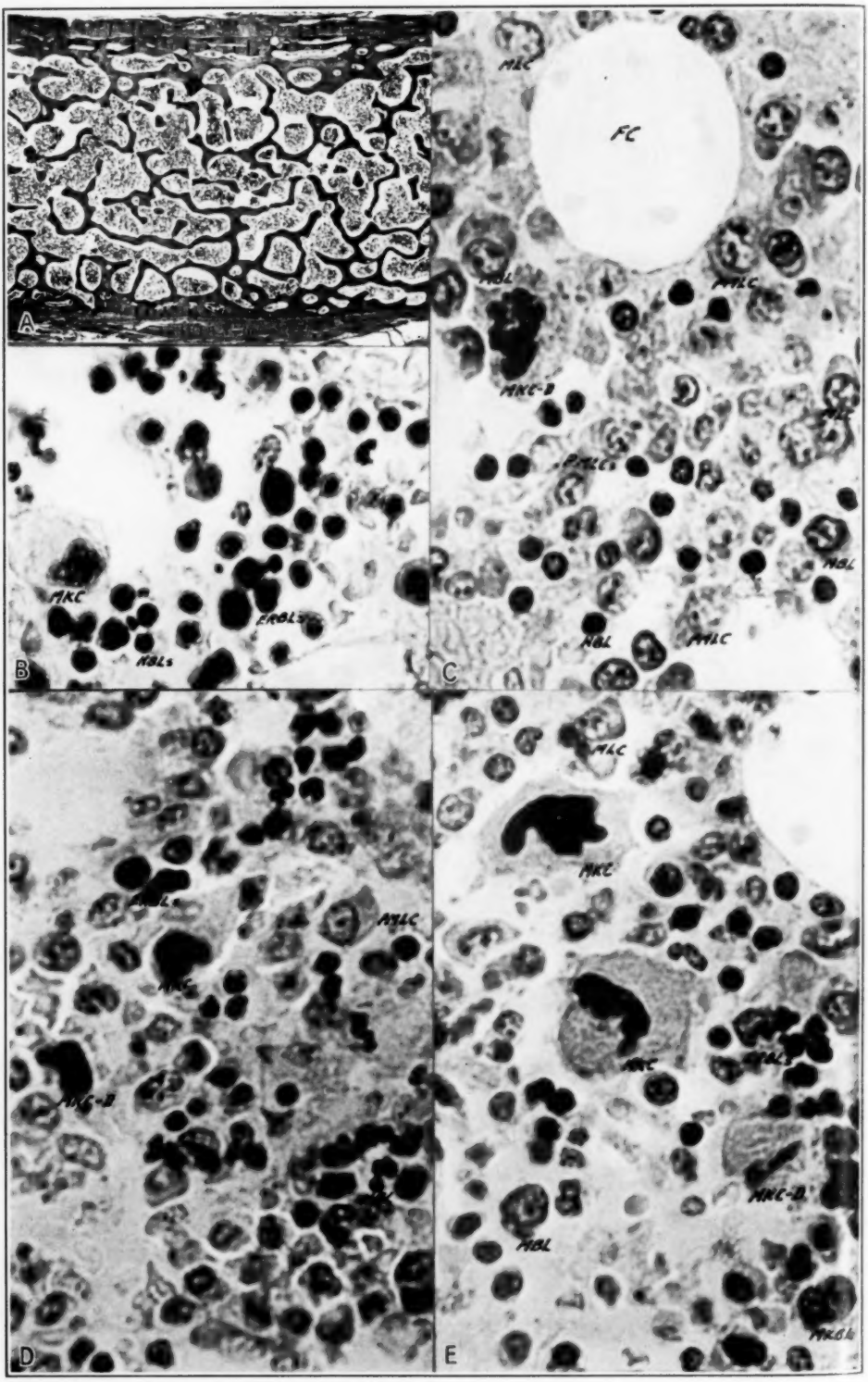

PLATE II.

cause at 10 months; minor bruises resulted in large hematomata and several minor cuts and a tooth extraction caused oozing for 6 weeks. Subject to frequent respiratory infections. *Family History:* Maternal grandfather, who died at 79 of other causes, had a number of prolonged bleeding episodes; oldest sons of two of his daughters were also bleeders, though in each case a daughter and another son were normal in this respect; the patient, an only child of the third daughter, was definitely hemophilic. *Physical Examination:* Undernourished child, moderately cyanotic and very toxic; lungs showed signs of consolidation over right upper and both lower lobes with few râles and suppressed breath sounds; heart sounds poor; no other findings of note. *Laboratory Tests* (obtained from admission to Mt. Sinai Hospital in 1931). Urine negative; Hgb. 75 to 50%; erythrocytes 3,680,000 to 2,630,000; leukocytes 11,700 (neutrophils 78%) to 10,900 (3700 during final illness). Blood calcium 11.7 mg.%; blood phosphorus 3 mg.%; bleeding time, 5½ minutes; coagulation time, 9 minutes, 35 seconds (no normal control done); platelets 260,000; blood Type III. *Course:* Pulse gradually weaker and death occurred 2 days after first symptom.

Necropsy: (U. H., '34–1316, 1 hour after death, Dr. D. R. Coman). Asthenic young male, height 144 cm., weight 32 kg., presenting pallor of skin and mucosæ; each pleural sac contains 100 cc. of serosanguinous fluid. *Aorta* is smooth, white, elastic and shows no abnormality of calibre or thickness. *Heart* appears normal except for dilatation of right chambers, weight being 160 gm. and left ventricular wall 1 cm. thick. *Lungs* present large irregular red patches over lower lobes, left weighing 310 gm., right 440 gm., cut surface showing solid, airless, hemorrhagic patches throughout left lower lobe and entire right lung, intervening parenchyma being gray and moist; pus exudes from small bronchial radicles. *Spleen* weighs 90 gm. with dark red, bloody pulp dotted by gray, pinpoint follicles. *Kidneys:* each weighs 100 gm. and shows no significant changes; lower urinary tract and genitalia are apparently normal. *Gastro-intestinal tract* appears normal throughout; mesentery contains a few bean-sized, firm, gray lymph nodes. *Liver*, weighs 1020 gm., is red-brown, firm and displays normal markings, blood oozing in moderate amount from cut surface; gall bladder and bile ducts show no gross lesions. *Pancreas, adrenals, thyroid, thymus* and *pituitary* appear normal; middle and internal *ears* and *brain* show no lesions. *Bone marrows* of femur, sternum and vertebra are soft and red, that from the tibia soft and yellow.

Histology. *Heart* shows degenerative changes of rather marked degree in the congested myocardium. *Lungs* are congested and edematous, sections of right upper and lower lobe presenting typical picture of extensive bronchopneumonia with early abscess formation and conspicuous masses of cocci; left upper lobe is the seat of early consolidation; a few naked nuclei of megakaryocytes lie in capillaries; pleura is covered in part by fibrinopurulent exudate. *Spleen* shows a comparatively cell-poor, blood-filled pulp dotted by relatively small follicles with ill-defined centers; vascular walls are slightly thickened and occasionally hyalinized. *Lymph nodes* of the mesenteric group retain essentially normal architecture, distorted through hyperplasia of reticulo-endothelial and lymphatic cell elements. *Kidneys* display glomeruli engorged with blood and tubular epithelium that is moderately degenerated. *Liver* epithelium is swollen and granular, nuclei being somewhat faded; Kupffer cells are not prominent; portal triads appear normal. *Pancreas* shows mild degenerative changes in alveolar epithelium. *Adrenal* cortical cells contain the usual amount of lipoid but show loss of cell outline accompanied by occasional nuclear pyknosis. No structural abnormality is demonstrable in the *pituitary*. *Bone marrow:* The sternum contains about 25% fat, cellular marrow being loose; engorgement of blood sinuses is particularly prominent. Cells of the erythropoietic series are in the foreground, seen mostly in the late erythroblastic and nor-

moblastic stages (Table 1). The neutrophil group is also active, myelocytes being the predominant type. Megakaryocytes are approximately twice normal in number, the usual degenerative-regenerative balance being maintained; nuclear morphology is about as diverse as that noted in the other cases. The vertebral marrow is somewhat more cellular, but the relative proportion of cells is approximately the same, megakaryocytes being perhaps somewhat more plentiful with fewer degenerate forms. The femur is conspicuous in the activity of the neutrophil progenitors, particularly the younger forms (myeloblasts and promyelocytes), as though the previously hypoplastic marrow has undergone hyperplasia in the direction of the immediate necessity of combating infection; megakaryocytes are also seen in predominantly blastic and normal forms (Table 2); the marrow is approximately 30% cellular. The tibia presents almost complete acellularity in the midportion of the diaphysis. Bloodvessel walls are normal.

TABLE 1.—DIFFERENTIAL MARROW COUNTS (PER CENT).
(Azure II-Eosin.) (500 cells each.)

	Case 1.	Case 2.	Case 3.		Normal control.
	Sternum.	Sternum.	Sternum.	Femur.	Sternum.
Undifferentiated cells	3.0	0.0	0.0	3.6	0.0
Granulocyte series.*					
Myeloblasts	3.2	5.4	2.2	12.6	0.6
Promyelocytes (neutrophil)	5.4	9.8	8.2	20.0	9.0
(eosinophil)	0.2	0.4	0.2	0.4	0.0
Myelocytes (neutrophil)	7.4	22.8	13.2	9.2	34.6
(eosinophil	1.8	4.6	1.4	1.0	2.0
Metamyelocytes (neutrophil)	13.8	6.0	4.8	4.6	14.6
(eosinophil)	0.4	0.8	0.4	0.2	0.0
Segmenters (neutrophil)	6.8	1.6	2.0	0.8	3.0
(eosinophil)	0.0	0.4	0.0	0.0	
	40.6	51.8	32.4	48.8	63.8
Erythrocyte series:					
Megaloblasts	3.8	0.2	0.4	0.8	0.0
Erythroblasts (early)	8.2	6.4	7.0	6.8	14.8
(intermediate)	8.6	15.2	10.8	8.0	
(late)	8.4	11.6	14.4	9.0	
Normoblasts	22.0	7.4	30.0	14.8	18.2
	51.0	40.8	62.6	39.4	33.0
Thrombocyte series:					
Megakaryoblasts	0.2	0.4	0.4	0.2	0.2
Megakaryocytes (normal)	0.6	0.2	0.4	1.6	
(degen.)	0.8	1.6	0.6	0.4	0.8
	1.6	2.2	1.4	2.4	1.0
Reticulo-endothelial apparatus:					
Reticular cells	3.6	2.8	1.8	3.6	2.0
Endothelial cells	0.8	1.0	0.0	1.4	
Wandering forms	0.4	0.6	1.2	0.4	0.2
	4.8	4.4	3.0	5.4	2.2
Lymphocytes	0.6	0.8	0.6	0.4	0.0

* Basophils not encountered; metamyelocytes include, for simplification, all cells between myelocytes and filamented nuclear forms.

Comment. A number of diseases other than hemophilia can produce "bleeders" and some of these have a familial incidence. However, in these 3 cases, even though hematologic studies are not all that might be desired, the diagnosis seems clear. The typical familial and individual history of bleeding episodes is reinforced by the delays in clotting time, which are all the more striking as they were done by the finger prick methods rather than with venous blood. The uncontrolled addition of tissue juice by the prick method shortens the clotting time, so that deficient blood may give a normal test.

If it is delayed by this method, however, it would be as much or more delayed with venous blood.

Among the reported necropsies on hemophiliacs may be mentioned those of Grandidier, Faucherand, Proby and Colrat, Ricker, Kissinger, Voit and Paus, Keneagy, Steward and Legg, the first and last authors furnishing a more complete group of references. While detailed descriptions are to be found of the size and location of hematomata, the pallor, perhaps degeneration of the organs and so on, little or no histology and absolutely nothing of significance about the hemopoietic organs is to be found, save for Ricker's statement that the vertebral and femoral marrows were not hyperplastic and Schmidt's reference to his postmortem examination of a case some years earlier which failed to reveal anything abnormal. His remark that nothing was yet known about the pathologic anatomy of hemophilia continued to be justified.

Though a discussion of the pathogenesis of hemophilia is beyond the scope of this paper, it may be briefly stated that for many years various factors have been held responsible for the bleeding. Virchow's authority for a long time focussed attention on Blagden's observation of unnatural thinness of vessel walls, an item that we have not observed in our 3 cases. Sahli postulated a local condition in the wall to account for the spontaneous hemorrhages, in addition to blood changes responsible for delayed coagulation of the blood, which, of course, is present even between attacks. Incriminated have been: (*a*) an excess of antithrombin (Weil), (*b*) calcium deficiency (Wright), (*c*) thrombokinase deficiency (Morawitz and Lossen), (*d*) qualitative defect in prothrombin (Nolf and Herry, Addis, Feissly and Freed, and Eagle) and (*e*) qualitative changes in the platelets (Fonio, Lee and Minot, Howell). The last two views have the most adherents today, the platelets on account of the morphologic changes noted and their observed delay in breaking up under experimental conditions, the prothrombin defect because a proper assemblage of components will produce normal plasma clotting with hemophilic platelets and under certain conditions hemophilic plasma still clots slowly when normal platelets are added. Quick's recent work tends to relieve prothrombin of responsibility. The matter still awaits elucidation; a possibility of both factors being contributory remains *sub judice*, especially in view of Howell's statement that platelets may contain prothrombin. Any information then, about the state of the hemopoietic tissues, especially of the megakaryocytes from which the platelets are derived, should be on record.

The state of the thrombocyte series in the bone marrow was the striking feature in all 3 cases, even though the cause of death was different in each. The extent of numerical increase in this series of cells was not fully appreciated until estimations of the incidence in approximately 12,000 cells per bone was compared with similar estimations in a group of non-hemophilic controls (Table 2). The

differences in the percentages of the thrombocyte group in Tables 1 and 2 indicate the need for an estimation covering a much larger number of cells than the usual differential count of 500 or even 1000 in categories that are sparsely represented; a method which we have found satisfactory is described briefly in the following article.

TABLE 2.—GROSS ESTIMATION OF THROMBOCYTE SERIES.*
(200 consecutive fields, averaging 60 cells each) (expressed as number per 12,000 total cells and in per cent of the 12,000).

	Megakaryoblasts.		Normal megakaryocytes.		Degen. megakaryocytes.		Total.	
	No.	%	No.	%	No.	%	No.	%
Hemophilia:								
Case 1.—Sternum	12	0.10	21	0.18	36	0.30	69	0.58
Vertebra	16	0.13	21	0.18	35	0.29	72	0.60
Case 2.—Sternum	7	0.06	6	0.05	32	0.27	45	0.38
Vertebra	8	0.07	26	0.22	25	0.21	59	0.49
Case 3.—Sternum	8	0.07	20	0.17	23	0.19	51	0.43
Femur	16	0.13	23	0.19	9	0.08	48	0.40
						Average	57.3	0.48
Non-hemophilic controls:								
Symptomatic purpura	6	0.05	10	0.08	15	0.12	31	0.26
Symptomatic purpura	1	0.01	2	0.02	15	0.12	18	0.15
Polycythemia vera	4	0.03	20	0.17	20	0.17	44	0.37
Chronic hemorrhage	4	0.03	9	0.08	13	0.11	26	0.22
Arsphenamin neutropenia	4	0.03	16	0.13	7	0.06	27	0.23
Third degree burn	5	0.04	12	0.10	13	0.11	30	0.25
Brain tumor	2	0.02	8	0.07	21	0.18	31	0.26
Bronchopneumonia	6	0.05	11	0.09	14	0.11	31	0.26
						Average	29.7	0.25

* For method employed see following article.

The relative percentage in the 3 hemophiliacs was fairly uniform and, surprisingly enough, in 2 cases the number in each of two different bones varied by only 3 cells. As shown by the larger cell count, the constancy of the megakaryocyte content of marrow in unselected non-hemophiliacs was remarkable, falling within a range of 5 cells except for a case of severe symptomatic purpura in profound pansinusitis which showed comparative paucity, and an increase in a case of polycythemia vera in which megakaryocytes are usually described as being plentiful. An average in hemophilia of 57.3 cells of the megakaryocyte series per 12,000 total cells opposed to 29.7 in 8 non-hemophilic controls is regarded as significant. It is worthy of note that the largest percentage of megakaryocytes appeared in the purely hemorrhagic case, the smallest in the purely infectious and a midposition held by the case in which hemorrhage was a minor factor; the increased incidence of megakaryoblasts, evidence of regenerative activity, was associated with hemorrhage, matched only by the apparently recently hyperplastic femur in the infectious case, in which the increase in young forms was offset by the sparsity of degenerate cells. Even in normal marrow a so-called degenerative-regenerative balance between normal and degenerate megakaryocytes is maintained and the close juxtaposition of a young and an effete cell occurring fairly frequently led one of us in a previous paper to suggest the possibility that the stimulus to new formation is furnished by a "nekrohormone" liberated by the degenerate cell.

The morphology of megakaryocytes in this disease does not vary from the normal. The megakaryoblast is seen as a hypertrophic,

moderately basophilic cell which may be strictly mononuclear or may exhibit early nuclear polymorphism, nuclear lobes occasionally appearing to lie one upon the other; the vague acidophilic granularity is rarely seen in this stage. The normal adult megakaryocyte presents a more or less vesicular nucleus which is multilobated with sharp perinuclear membrane, fine chromatin strands and prominent nucleoli lying in a large cytoplasmic mass with pale basophilic background and extremely delicate pink-staining granules. The degenerate cell is characterized by a shrunken or faded nucleus and a frayed vacuolated cytoplasm which stains poorly. On four occasions it was possible to demonstrate the so-called "Wright's figures," *i. e.*, cytoplasmic buds of megakaryocytes which extend through the wall of a blood sinus into the lumen, confirming J. H. Wright's observations on the mechanism of platelet formation; two such cells are pictured (Plate I, *A* and *B*).

Formation of erythrocytes and granulocytes in all 3 cases conformed strictly to normal standards. Erythropoiesis seemed rather more active in the flat bones of all 3 cases than one usually finds except in the severe anemias. The femur of Case 3 offered a contrast in that red blood cell formation was subordinate, as though hyperplasia in the long bones occurs as the needs of the situation demands, in this instance the production of neutrophils to combat infection. Eosinophilic myelocytes were unduly prominent in the marrow of Case 2, the reason not being apparent. Cells of the general reticulum appeared normal and transition toward megakaryoblasts and myeloblasts could be traced. The marrows were too complex for the demonstration of Doan's capillaries. Although the femur in Case 3 was moderately hyperplastic, the tibia was entirely fatty, supporting the view that the femur is a fairly good index of increasing bone marrow activity, and that the tibial marrow is among the last to become hyperplastic.

Details of various visceral changes are not worthy of comment except for a few points. It can be safely stated that no structural abnormality of bloodvessels can be demonstrated; the vascular thickening and distortion in Case 1 were undoubtedly rheumatic. The accessory blood-forming organs, namely spleen and lymph nodes, showed no significant changes, although an increased prominence of cells of the reticulo-endothelial system was noted in each case; there was no evidence for or against the autochthonous formation of the megakaryocytes seen in the spleen of Case 1; naked megakaryocyte nuclei were observed in the lung and kidney capillaries, indicating that they, at least, were embolic. Megakarocytes in the blood stream and in organs other than the bone marrow have, however, been observed in various conditions.

Summary. 1. Three fatal cases of hemophilia with necropsy are reported, 1 dying from uncomplicated hemorrhage, 1 from appendicitis and hemorrhage, and 1 from fulminating penumonia.

2. The hemopoietic tissues all showed normal regenerative ability, the first two predominantly erythroblastic, the third leukoblastic.

3. All three showed a marked increase of megakaryoblasts and megakaryocytes in the bone marrows, indicating a relationship of the blood platelets to the hemophilic process.

4. J. H. Wright's observation of platelet formation in the bone marrow sinusoids from intruding pseudopods of megakaryocyte cytoplasm was supported by our findings.

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A NOTE ON DIFFERENTIAL CELL COUNTS OF BONE MARROW.

With Special Reference to the Estimation of Infrequently Appearing Cell Types.*

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The differential count of cells of the bone marrow is not a simple matter, particularly when one is dealing with sectioned material.

* No. VI of the "Studies on the Structure and Function of Bone Marrow."

For those accustomed to the study of blood films, the marrow count is comparatively easy when obtained from well prepared smears (teased tissue suspended in serum and streaked as with blood) or imprint preparations (bits of marrow touched to the slide) stained by the method routinely used with blood. Unquestionably individual cell morphology is best brought out by this method. If one is concerned with the relative proportions of various cell series, however, the smear or imprint preparation is not accurate, in that closely packed cell clumps do not tend to disperse or may even adhere to marrow interstices and not be included on the slide. We believe that careful differential counts of marrow sections give truer information regarding the status of the hemopoietic tissue.

Of necessity, thin sections well stained by one of the Romanowsky modifications (azure II-eosin, eosin-methylene blue, eosin-orange G-toluidin blue, dilute Giemsa, etc.) must be employed. The optical system of the microscope should be such that a magnification of about 1500 diameters is attained, for example, with a 1.2 mm. oil-immersion objective and a 15× ocular; the higher magnification is of particular importance in that there are fewer cells per field, thus admitting less possibility of confusion. An ocular micrometer is practically a necessity and may be either of the net type or the two-parallel-line variety, the latter being the one usually employed in reticulocyte estimations; the choice is a matter of personal taste.

TABLE 1.—COMPARISON OF COUNT OF FIRST AND SECOND 500 CELL GROUPS.

	Best fit.*				Poorest fit.†			
	First 500.		Second 500.		First 500.		Second 500.	
Granulocyte series:								
Myeloblasts	175		185		25		11	
Promyelocytes (neutrophil)	14		12		36		24	
Myelocytes (neutrophil)	1		1		73		115	
Myelocytes (eosinophil)	0		1		9		3	
Metamyelocytes (all types)	0		0		67		89	
Segmenters (all types)	0		0		162		100	
	—	190	—	199	—	372	—	342
Erythrocyte series:								
Megaloblasts	19		16		0		2	
Erythroblasts	92		95		32		60	
Normoblasts	102		97		43		61	
	—	213	—	208	—	75	—	123
Thrombocyte series:								
Megakaryoblasts	4		7		2		0	
Megakaryocytes	7		7		4		2	
	—	11	—	14	—	6	—	2
Reticulo-endothelial apparatus:								
Reticular cells Endothelial cells	50		47		18		14	
Wandering cells	4		9		23		15	
	—	54	—	56	—	41	—	29
Lymphocyte series:								
Lymphocytes	23		19		5		3	
Plasmocytes	9		4		1		1	
	—	32	—	23	—	6	—	4

* Case of idiopathic agranulocytosis.
† Case of septic neutropenia.

Differential Count of All Cell Types. Until recently we regarded a count of 1000 cells as none too extensive. Comparison, however, of the percentage obtained in the first 500 cells with that of the second showed, to our considerable relief, negligible difference for the more frequently represented cell types; Table 1 lists the best and poorest examples now on hand.

Identification and tabulation, then, of 500 cells are deemed sufficient. Dr. Neil McLeod tells us that he has had the same experience and agrees that 500 is the optimum number for the chief groups.

The procedure is best (but not necessarily) carried out by two individuals, an observer and a recorder, the former tallying total cells on a hand tabulator. The list of cell types to be identified is prepared beforehand and the recorder tabulates the cells as called. The number of cell varieties is too great to permit the use of any instrument such as the Marbel blood cell calculator. In a given delineated field all cells of a particular type may be counted and the total given to the recorder before passing on to the next cell type in the list, or cells may be tallied as they are met by proceeding systematically through the field.

An effort is necessary to eliminate as far as possible the personal factor in the count, *i. e.*, the subconscious temptation to stop at choice fields containing perhaps particular cell types in which the observer is interested. Our habit is to count every fourth field, avoiding only those containing bone trabeculæ or large blood sinuses. The interpretation of cell morphology varies slightly with different individuals and the terminology employed by the three main schools of hematology is considerably at variance; comparison, therefore, is most reliable when the marrow counts have been done by the same observer.

About 5% of cells encountered cannot be identified accurately and are best completely omitted rather than listed by guess; this figure varies in direct proportion to the degree of degeneration present in the tissue. If the number is unduly large, a statement to this effect should be made in the report.

Estimation of Infrequently Appearing Cells. The ordinary count of 500 can hardly represent accurately the incidence of a type of cell which is sparsely and irregularly distributed in the tissue. A method of estimation involving many fields and great numbers of cells would naturally narrow the limits of error. In the previous article, for example, the cells of the megakaryocyte group were under surveillance; empirically we decided to note the incidence of these cells in 200 consecutive fields. All cells in each of 10 fields were counted in each of the 14 marrows studied by this method and an average obtained (for the optical system employed the average was 60 [59+] cells per field with a scatter from 49 to 70); this was further checked from time to time; thus the number of megakaryocytes in 200 fields (*i. e.*, approximately 12,000 cells total) was

recorded and the percentage calculated. Encroachment of fat cells, bone trabeculæ and blood sinuses on the field is avoided as much as possible; when fat is plentiful, half-fields can be estimated. The constancy of these figures was remarkable, much more so than that shown in the full differential count of 500 or even 1000 cells, demonstrated clearly by comparison of Tables 1 and 2 in the preceding article.

We feel that the similarity of the megakaryocyte percentages in the control cases constitutes support for the validity of this method.* It is obvious, however, that averages must usually be obtained for each marrow studied, and that if the cellular density of the fields varies greatly in any one marrow, the method is not suitable. The error involved in taking an average number of cells per field appears to be much smaller than that incurred by examining the smaller number of cells. Thus, if the maximum observed variation of figuring on 50 cells per field instead of 60 (or an estimation error of about 16%) was assumed in the sternal marrow of Case 3 (see preceding paper), the percent of megakaryocytes would only be changed from 0.43 to 0.51, whereas the 500 cell method gave 1.4%.

CHRONIC GRANULOCYTOPENIA OF FIVE YEARS' DURATION WITH RECURRENT ACUTE ATTACKS.

CASE REPORT.

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BECAUSE of the widespread interest in granulocytopenia (agranulocytic angina, malignant neutropenia, granulopenia), I am reporting a case of chronic primary granulocytopenia which has been under my observation for 5 years. The chief value of the study lies in the length of time the case has been under observation; the blood counts made daily or at regular intervals over this period of time; and the complete picture it presents of the chronic primary type of the disease—the characteristics of the acute episodes, the subjective and objective findings before, and during the intervals between, attacks, and the blood pictures during the various periods of the cycle of the disease.

Case Report. The patient, a woman, aged 33, had never consulted a physician prior to this illness. After the sudden death of her first husband,

* For those who wish to get accurate percentages of sparse cell types and mistrust a method based on an average number of cells in fields that may vary considerably, it is suggested that after the 500 cell count has been finished, the count be continued without allocation of cell types other than those under special consideration, depending on the patience of the observer, until at least 5000 cells have been covered.

in 1927, she had noticed periods of extreme exhaustion in which she seemed to need more rest than usual, but she attributed this exhaustion to irregular hours of eating and resting following his death.

In November, 1929, 5 months after her second marriage, she had a very profuse menstrual period accompanied by cramping pain in the pelvis. Because of amenorrhea for the preceding 3 months and severe nausea of 1 week's duration, this was diagnosed by a gynecologist as a spontaneous abortion. Codein and morphin were given for relief of the pain and, as the uterine bleeding persisted, gynergen and ergot were administered; aspirin, allonal, amytal and sodium luminal were prescribed for restlessness and general aching. One week later she experienced chilly sensations, pain in the eyes and the feeling that her head was expanding. The next day she had a definite chill. She consulted no physician at that time but took large amounts of allonol. Three days later I saw her for the first time.

Besides the generalized aching and chilly sensations, the patient complained of pain over the precordial area, pain in and around the eyeballs and sharp, shooting pains in the long bones. The uterine hemorrhage and pelvic pain had completely subsided. Her temperature was 102° F. A diagnosis of influenza was made, but because of the possibility of an early encephalitis a neurologist was consulted and a spinal puncture was done. The spinal fluid was normal in all respects. The 5 blood counts made at this time, November 11 to 18, 1929, revealed a depression of the total leukocyte count, and upon 1 occasion an almost complete absence of neutrophils (Table 1).

During the first half of 1930 the patient had a urinary disturbance characterized by dysuria with considerable albumin and numerous pus cells in the urine. She had no other symptoms and experienced no other disturbance. During 1931 she had no symptoms of sufficient importance to cause her to consult a physician. The findings of an occasional urinalysis were normal.

On January 12, 1932, another attack similar to that of November, 1929, occurred (Table 1). She recovered from this attack but continued to complain of exhaustion, aching and occasional rises in temperature.

On April 13, 1932, the patient experienced a sudden severe chill with a temperature of 103° F. Her appearance was that of a desperately ill person. A blood count revealed the presence of only 800 leukocytes, of which but 4% were neutrophils. She was sent immediately to the hospital where nucleotide was given according to the directions of Jackson and his coworkers with results in accord with their experience. The course was a stormy one but the apparent response to the nucleotide, though gradual, was continuous (Table 1). A culture from the blood taken during this attack disclosed the presence of an organism later identified as a diphtheroid streptococcus. Shortly after the attack the organism was recovered also from the cervical canal.

The syndrome of aching, easy fatigue, precordial pain with slight irregularity of the pulse, periods of loose stools and occasional rises in temperature persisted.

A complete physical reëxamination now revealed three possible sources of infection: cervix, right tube and appendix. Because of the possibility that infection might be playing a part in her condition it was recommended that the cervix be cauterized, which was done, and that the pelvis and appendix be investigated as soon as the condition of the patient should permit such a procedure.

On November 2, 1932, another acute attack occurred. Nucleotide was given again and again apparent response was noted in increasing numbers of leukocytes and a gradual return of neutrophils (Table 1).

A month later, as the patient felt very well subjectively, an abdominal

exploration preceded by a curettage of the uterus was performed. The cervical os was somewhat stenotic as a result of previous cauterization. The abdominal organs were normal in appearance and to palpation and no gross lesions could be found. Both ovaries and both tubes were normal in appearance as was the uterus. Appendectomy was performed.

Following the surgical procedure a typical postoperative leukocytosis with the usual postoperative neutrophilia developed (Table 3). The leukocyte count then returned to normal limits but the neutrophils and lymphocytes again assumed their previous fairly equal distribution.

In February and May, 1933, she experienced sufficient increase in symptoms and change in blood count to cause us to curtail all activity and put her at bed rest, although the expected acute attacks did not develop. The last acute episode to date occurred in September, 1933, following an acute cold (Table 1). No medication other than general supportive measures was used.

Discussion. The symptomatology, the clinical history, the physical findings and the blood counts taken during the acute attacks (Table 1) and during the periods of remission (Table 2) present a typical picture of the chronic primary type of the disease without ulceration.

TABLE 1.—BLOOD COUNTS MADE DURING ACUTE ATTACKS.

Date.		Leukocytes.	Neutrophils, %	Lymphocytes, %
11/12/29		5200	40	40
11/13/29		5600	35	61
11/14/29		3400	9	86
11/15/29		3800	6	84
11/18/29		7200	27	71
	Supportive Treatment Only.			
1/12/32		2000	0	97
1/13/32		2100	3	94
1/14/32		2600	16	82
1/18/32		7400	40	56
1/21/32		4800	28	67
1/25/32		6000	64	34
	Supportive Treatment Only.			
4/12/32		800	4	96
4/13/32	12 M.	700	0	97
	2 P.M.	700	0	94
	4 P.M.	850	0	98
	6 P.M.	800	0	93
4/14/32	8 A.M.	880	0	93
	10 A.M.	840	2	95
	12 M.	1300	2	90
	2 P.M.	1300		
	4 P.M.	1300	3	90
	6 P.M.	1750	7	91
4/15/32	8 A.M.	1700	14	86
	12 M.	1600	45	54
	5 P.M.	1700	16	83
4/16/32	6 A.M.	2280	35	65
	12 M.	1700	33	66
	5 P.M.		32	68
4/17/32	8 A.M.	2850	38	62
	12 M.	2400	33	67
	5 P.M.	2430	21	72

TABLE 1.—BLOOD COUNTS MADE DURING ACUTE ATTACKS.—(*Continued.*)

Date.		Leukocytes.	Neutrophils, %	Lymphocytes, %
4/18/32	8 A.M.	2480	30	66
	12 M.	2850	27	65
	5 P.M.	2620	21	78
4/19/32	8 A.M.	2700	31	
	5 P.M.	3206	35	64
4/20/32	A.M.	3730	34	66
	P.M.	4410	31	77
4/21/32	A.M.	3950	44	56
	P.M.	4550	31	68
4/22/32	A.M.	4500	45	53
	P.M.	4100	23	74
4/23/32	A.M.	4100	42	58
	P.M.	4500	45	52
4/24/32	A.M.	5250	48	48
	P.M.	5400	50	46
4/26/32		7400	45	50
		9100	49	45
		Nucleotide Therapy.		
10/31/32		6500	52	44
11/ 2/32	A.M.	3400	73	27
	P.M.	3000	79	21
11/ 3/32	A.M.	1700	26	68
	P.M.	1200	12	84
11/ 4/32	A.M.	1500	2	89
	M.	1400	0	93
	P.M.	1100	0	100
11/ 5/32	A.M.	1300	1	95
	P.M.	1200	5	88
11/ 6/32	A.M.	2600	21	72
	P.M.	2200	24	71
11/ 7/32	A.M.	3200	52	46
	P.M.	3200	46	52
11/ 8/32	A.M.	3200	45	53
	P.M.	3500	44	54
11/ 9/32	A.M.	3600	42	57
	P.M.	4600	39	59
11/10/32		4700	49	47
11/11/32		6400	59	37
		Nucleotide Therapy.		
9/11/33*	9 A.M.	2400	6	48
	11 A.M.	2600	6	53
	1 P.M.	4050	2	70
	3 P.M.	4150	4	62
	5 P.M.	5000	8	64
	7 P.M.	5250	7	60
1/12/33	9 A.M.	6100	14	57
	11 A.M.	6000	12	61
	1 P.M.	4950	8	76
	5 P.M.	5650	14	57
9/13/33	9 A.M.	4950	13	73
	11 A.M.	5800	17	58
9/14/33		8500	17	58
9/18/33		10,300	57	42
		Supportive Measures Only.		

* I am indebted to Dr. S. R. Mettier of the University of California Hospital in San Francisco for the blood counts and data obtained during this attack which occurred while the patient was visiting in that city.

TABLE 2.—BLOOD PICTURES DURING PERIODS OF REMISSION.
(Averages of Counts Made.)

Date.	Leukocytes.	Neutrophils, %	Lymphocytes, %
2/ 9/32 to 3/24/32 (14 counts)	6521	48	48
4/28/32 to 10/ 5/32 (25 counts)	8128	57	39
11/12/32 to 12/ 3/32 (daily counts)	5643	38	56
12/14/32 to 1/31/33 (daily counts)	7756	43	53
2/11/33 to 4/24/33 (daily counts)	7494	46	48
5/10/33 to 9/ 7/33 (45 counts)	7064	44	52
9/19/33 to 1/16/34 (23 counts)	9321	54	41
2/ 1/34 to 6/ 1/34 (38 counts)	6154	55	40
6/ 1/34 to 12/31/34 (28 counts)	6135	59	35

TABLE 3.—NORMAL POSTOPERATIVE LEUKOCYTOSIS.

Date.	Leukocytes.	Neutrophils, %	Lymphocytes, %
12/ 4/32*	8,800	37	54
12/ 5/32	10,100	47	41
12/ 6/32	11,400	63	32
12/ 7/32	12,000	78	16
12/ 8/32	9,500	72	26
12/ 9/32	8,500	66	27
12/10/32	8,200	55	39
12/11/32	9,000	57	36
12/12/32	8,000	43	54
12/13/32	6,775	52	43
12/14/32	8,800	40	57

* Date of operation.

TABLE 4.—INCREASE IN NEUTROPHILS FOLLOWED BY REVERSAL OF NEUTROPHIL-LYMPHOCYTE RATIO—A POSSIBLE INDICATION OF ONCOMING ACUTE ATTACK.

Date.		Leukocytes.	Neutrophils.	Lymphocytes.
10/31/32		6500	52	44
11/ 2/32	A.M.	3400	73	27
	P.M.	3000	79	21
11/ 3/32	A.M.	1700	26	68
	P.M.	1200	12	84
11/ 4/32	A.M.	1500	2	89
2/ 3/33		7100	47	50
2/ 4/33		7500	63	33
2/ 5/33		5600	74	25
2/ 6/33		4000	32	63
2/ 7/33		6200	19	71
2/ 8/33		5800	28	66
2/ 9/33		6400	47	50
2/10/33		8900	45	50
4/29/33		7500	53	43
5/ 1/33	A.M.	4900	61	37
	P.M.	2600	37	58
5/ 2/33	A.M.	2400	16	79
	P.M.	4300	10	82
5/ 3/33		5000	19	79
5/ 4/33		7200	39	59
5/ 5/33		6400	37	59
5/ 6/33		7800	52	40
5/ 8/33		7700	49	48

The blood pictures reveal one finding of particular interest. On 3 occasions (November 2, 1932, February 5, 1932, May 1, 1932) an increase in neutrophils was noted a few hours before, after or at the same time that the total leukocyte count started to fall (Table 4). The fall of the neutrophil count from this higher point was abrupt and caused a complete reversal of the neutrophil-lymphocyte ratio. It is possible that such an increase in neutrophils may be used as an indicator of an oncoming acute attack.

Because of a possible relationship between certain drugs and granulocytopenia, in April, 1933, the patient was asked to discontinue all drugs of the benzin ring. At this time she told me that she had done this voluntarily after the first acute attack in 1929, as she thought that the allonol which she had taken in large amounts at that time might have been responsible for the blood picture.

Nucleotide was given in 2 of the most severe attacks. The rise in the leukocyte and neutrophil count corresponded to the results apparently obtained by its use by Jackson. Supportive measures only were used during the other less severe attacks.

During the periods of remission various forms of medication have been tried. An autogenous vaccine from the diphtheroid streptococcus found in the blood stream and cervical canal resulted in no apparent improvement. Antuitrin intramuscularly and thyroid extract orally were given over a period of several months because of irregularity of menstruation and the fact that her first definite attack occurred with a delayed menstrual period and presumed abortion, and because a possible connection between this disease and glandular imbalance has been suggested by some authors. This form of therapy produced no apparent change in symptomatology or blood picture. Bone marrow was given and was discontinued after a month's trial, during which no improvement was noted, because of untoward symptoms of nausea, vomiting and dysentery.

Concentrated forms of vitamins B and D, in addition to a well-balanced diet, have been given empirically since June, 1934. During this time there has been apparent improvement in subjective symptoms and a rise in the general level of the leukocytes and the neutrophil-leukocytes to within normal limits. We are continuing this line of treatment on the basis that granulocytopenia may be a deficiency disease in the same way that pernicious anemia is a deficiency disease. However, until the question of the etiology of the disease is determined by further observations and experimental work, our treatment can be only empirical and its value determined by results obtained.

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CYTOPLASMIC CHANGES IN THE PERIPHERAL NEUTROPHIL AS AN AID IN DIAGNOSIS AND PROGNOSIS.

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Our purpose is to call attention to a hematologic finding which we feel to be of proven clinical importance as an aid in diagnosis and prognosis and as a guide to the course of infectious disease. Except for a few American investigators (Kugel and Rosenthal,[1] Rosenwasser and Rosenthal,[2] Rosenthal and Sutro,[3] and Sutro[4]), this matter has been neglected in our country, though utilized to advantage by continental, particularly German, workers. Recent textbooks of hematology in our language fail to treat the subject adequately. Adler,[5] commenting upon the vast amount of clinical information to be gained by this examination of the blood, deplored the fact that alterations in the cytoplasm of neutrophils had been studied less than those of the nuclei.

Cytoplasmic changes in the peripheral neutrophil, as we have studied them, consist briefly of an alteration of the staining quality of the cytoplasm and its components from a normal eosinophilic pink to a dirty gray or blue. There is also usually an increase in granulation. In the normal neutrophil the cytoplasmic granules are fine, regularly dispersed and oxidase positive. In the abnormal cell they are coarse, irregular in distribution, staining a deep blue and oxidase negative. They may be sparse, grouped on one side, or diffusely scattered over the entire protoplasm. All the neutrophils are not uniformly granulated. In some the granules may be so large that the cell may be mistaken for a basophil. In addition, vacuolization of the cytoplasm is usually observed, giving the cells a moth-eaten appearance about the periphery or throughout the cytoplasm. These three changes, alteration of the staining character of the cytoplasm, abnormal granulation and vacuolization, have been regarded by most authors on the subject as toxic or degenerative changes, indicative of severe disease process, and when pronounced and progressive, to denote an unfavorable prognosis.

As early as 1908, Cesaris-Demel[6] spoke of these changes as degenerative, the vacuoles being due to loss of fat content of the

protoplasm; the poor staining quality he noted in cells "about to die" and termed it a process of autophagocytosis. He also observed the excessive granulation and regarded the prognosis as always improved when it disappeared from the cells. Türk[7] offered a complete description of toxic changes in granular leukocytes in various diseases in 1912. Mommsen,[8] with a special Giemsa stain diluted with a buffered solution of pH 5.4, showed that normal granules stained weakly compared to these abnormal granules. He termed the latter "pathologic or toxic" and stated that pathologic granulation is a measure of the intensity of the infection afflicting the patient. Barta[9] showed that one could differentiate by a study of these changes between localized and generalized infection and that increasing toxic cytoplasmic changes indicated increasing gravity of outlook. It is interesting to note that, in 1923, just 2 years before Minot and Murphy's discovery of liver treatment for pernicious anemia, at a time when such theories as infection by various organisms, particularly B. welchii and B. coli, were considered in discussions of the etiologic nature of this disease, Naegeli,[10] impressed with the persistent absence of pathologic alterations of the cytoplasm of the neutrophils in pernicious anemia and their frequent presence in infectious processes stated: "This finding alone is sufficient to convince me that the cause of pernicious anemia is not infectious." He[11] is so convinced of the regularity of this finding in severe infections that he uses its absence to militate against the belief of the infectious origin of acute leukemia. He further feels that the regularity with which these granulations occur in the neutrophils seen in agranulocytosis point to an infectious origin of this disease.

Spaeth[12] demonstrated with Mommsen's technique that in various infectious diseases the occurrence of pathologic cytoplasmic changes depended on the intensity of the infecting agent; the more virulent the latter the greater the toxic alterations of the cells. He also showed that the Schilling-Arneth shift did not always parallel these toxic changes. Matis,[13] corroborating this, maintained that when the toxic granulation is marked one must think not only of an infection but must consider a very grave prognosis. Adler[5] believes the granulation is due to absorption of toxin or to destruction of protein material, and in the graver septic conditions he finds vacuolated cytoplasm. Gloor[14] has done extensive work upon the subject. He has described two types of granules in infections; in mild cases the small granule now known as the "A granule of Gloor," and in severe cases the coarse, heavy granule known as the "B granule of Gloor." The bodies described as the Döhle bodies in scarlet fever, Gloor attributes to a toxically induced alteration in the staining quality of the neutrophil cytoplasm.

As to the nature of these changes, Naegeli[10] has pointed out that they do not occur in the bone marrow but only in the cells of the

circulating blood. A toxic effect upon the bone marrow usually produces alterations in the nuclei of the neutrophils. He finds cytoplasmic changes occurring in diseases particularly affecting mesenchymal tissues and states that the leukocytic cytoplasmic changes parallel the mesenchymal damage. Gloor demonstrated that the degree of absorption of pathologic substance from inflammatory foci had more to do with the pathologic cytoplasmic changes than the apparent local severity of the disease process. The greatest degenerative changes, for instance, were found near the crisis in pneumonia, when the greatest absorption of toxic products occurs. He further found that the more extensive the absorbing surface in a disease process the greater the toxic changes in the neutrophilic cells; hence in localized infections as appendicitis there would occur fewer cytoplasmic changes; whereas in peritonitis, with a large absorptive surface, marked toxic changes occur. In empyema, as the disease process becomes older and more encapsulated, the pathologic blood cytoplasmic changes become less pronounced, presumably because the pleural surface becomes less absorptive.

Schilling[15] attributes these cytoplasmic changes to degenerative phenomena, while Naegeli feels they are due to toxic effect associated with suppuration. Barta suggests that they represent phagocytosed particles. Their exact nature is still debatable. Quite recently, however, Hirschfeld and Moldowsky[16] report having found pathologic granular changes in the neutrophils of normal healthy Roentgen ray workers; hence they conclude the phenomenon is by no means a pathologic one, but rather a reactive change occurring in infection and under such influences as the Roentgen ray.

Present Study. Our study consists of a group of 250 cases of infectious and non-infectious diseases from the wards of Mount Sinai Hospital on which 1500 examinations were made, employing the Jenner-Giemsa staining method. We used Rosenthal's degenerative index, an excellent simple method for quantitatively measuring this phenomenon. The index is the percentage obtained by dividing the number of abnormal neutrophils by the total number of neutrophils studied in the smear. In general, our findings coincide with those of other authors, except those of Hirschfeld and Moldowsky. We have been unable to demonstrate these abnormal cytoplasmic states in Roentgen ray workers or in patients receiving Roentgen ray treatment. However, we have examined only a limited number and intend later to investigate the subject more thoroughly. At present we wish to report the findings in the diseases studied and indicate the value from a diagnostic and prognostic viewpoint derived from this study.

Pneumonia. This disease, above all others, is most uniformly characterized by cytoplasmic neutrophilic changes with high degenerative indices. Indeed, the frequency with which this phenomenon is present in lobar and severe lobular pneumonia should make one

hesitant in diagnosing these conditions in the absence of toxic granulation. The persistence of a high percentage of cells showing toxic cytoplasmic changes for some time after the crisis should warn the attending physician of a grave complication. During the crisis these changes frequently increase, but they slowly decrease and finally disappear with convalescence. We have studied 43 such cases: 25 of lobar pneumonia, 10 of lobular pneumonia, 2 diagnosed clinically pleural pneumonia, 1 diagnosed metastatic pneumonia, 1 diagnosed pneumonitis and 4 cases of empyema.

Lobar Pneumonia. Of the 25 cases, 20 yielded degenerative indices of 50% or more, with 5 less than 50%—1 with 0%. However, this latter patient was diagnosed lobar pneumonia by an unsatisfactory bedside Roentgen ray, the clinical course not bearing out the diagnosis. Nevertheless, including all cases, the average degenerative index found by us in lobar pneumonia was 60%. In many cases the degenerative index was more informative of the patient's condition than the total leukocyte count.

Pneumonia Series.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
L. S.*	77	16.0–19.0	98–100
F. C.*	45	4.4–11.5	34– 83
M. N.*	2	47.0–29.0	87– 61
A. S.*	27	9.0–27.9	90– 76
Y. G.*	60	17.8	63
H. O.*	45	18.0	83
S. M.*	76	29.7	17
J. R.	50	19.2– 8.2	68– 20
M. S.	23	23.8–12.9	51– 5
W. H.	2	20.4–19.3	90– 20
E. M.	3	17.3–13.2	15– 0
S. H.	8	17.0–10.2	50– 31
S. L.	20	32.1–14.2	13– 0
A. L.	5	26.7– 7.9	70– 62
E. B.	20	11.4– 7.2	90– 0
S. F.	1	25.6–12.2	76– 25
R. N.	7	29.5–15.5	52– 0
J. G.	6	25.8–16.5	31– 14
S. B.	14	31.4– 8.9	55– 0
D. G.	4	23.7–14.6	92– 74
F. A.	19	20.4	84
E. W.	22	17.0	58
I. S.	2	17.5–15.2	61– 50
J. F.	50	11.1– 7.1	0
D. H.	3	22.3– 9.0	83– 46

* Died.

Illustrative Cases. Case 1.—F. C., male, aged 45, was admitted to service of Dr. A. I. Rubenstone, on February 23, 1934, having been ill for 2 days prior to admission with fever, dyspnea, cyanosis and stitch-like pain in left lower chest. Temperature, 101.6° F.; pulse, 120; respirations, 36 per minute. Clinical diagnosis: Lobar pneumonia involving left lower lobe. C. B. C.: 93% hemoglobin, 4,770,000 erythrocytes, 4400 leukocytes, with 42 non-segmented and 52 segmented neutrophils and 6 lymphocytes. Degenerative index, 34%. Roentgen ray examination confirmed clinical

diagnosis. Artificial pneumothorax therapy was used; 500 cc. of air was injected into the left pleural space and repeated within 12 hours. Next day the general condition was poorer, temperature and toxicity persisted, the total leukocyte count was 7900 with 55 non-segmented and 40 segmented neutrophils. Degenerative index, 45%; on the following day, February 25, he was worse; the total leukocytes were 11,500 with 59 non-segmented and 38 segmented neutrophils; the degenerative index had risen to 83%. He expired on this day.

Case 2.—E. B., male, aged 20, was admitted to the service of Dr. A. I. Rubenstone, on February 27, 1934, for chill, pain in chest aggravated by deep breathing, cough and blood-tinged sputum. Temperature, 104° F.; pulse, 100 to 120; respirations, 28 per minute. Clinical diagnosis: Lobar pneumonia of left lower lobe, confirmed later by bedside Roentgen ray examination. Blood chemistry and serology normal; blood culture sterile. Sputum: Type I pneumococcus. Blood count: 87% hemoglobin, 4,300,000 erythrocytes, 11,400 leukocytes with 1 myelocyte, 32 non-segmented and 55 segmented neutrophils, 7 lymphocytes and 5 monocytes. Degenerative index, 40%. The following day the total leukocyte count rose to 18,300, differential similar to original examination, and degenerative index 55%. He was given 80,000 units of antipneumococcic serum (Type I) within 24 hours in addition to usual supportive measures. The next day, March 1, total leukocyte count was 17,900, differential same and degenerative index now 90%. Clinical condition remained unchanged. On March 2, temperature fell sharply to normal by crisis and remained there. On March 6, after steady improvement, total leukocyte count was 12,800 with 17 non-segmented and 62 segmented neutrophils. Degenerative index had dropped to 48%. On March 12, a slight leukocytosis persisted but the degenerative index reached 0%. On March 15, patient was discharged as cured—leukocyte count now normal and degenerative index 0%.

Lobular Pneumonia. In these 10 cases the degenerative index followed the clinical picture as accurately as did the temperature and more accurately than did the total leukocyte count. Four cases had degenerative indices of 50% or more, 5 cases had less than 50% and 1 case showed no toxic cytoplasmic changes. The average degenerative index was 45%, or 15% less than in lobar pneumonia. Cases of lobular pneumonia in children demonstrated the highest toxicity in the neutrophils in this series.

Lobular Pneumonia Cases.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
I. K.*	3	16.0–6.2	5–91
J. M.*	2	33.4	62
S. S.	1	37.0–17.2	72–27
M. G.	1	21.2	62
L. B.	1	12.7	35
M. L.	34	8.5–18.0	45–0
M. J.	7	15.4–10.5	16–0
W. B.	21	9.5	0
B. L.	65	7.8–5.6	30–0
J. S.	56	10.5–6.8	9–20

* Died.

Pleural Pneumonia. This is a term used by some clinicians to designate a form of pneumonitis characterized by fever, mild

toxicity, diminished breath sounds, questionable impairment and râles of pleuritic rather than parenchymal origin, *i. e.*, in which a diagnosis of consolidation cannot be made. These patients are usually not as ill as the cases classified lobar or lobular pneumonia and the diagnosis of pneumonia in them is always doubtful. Occasionally a mild pneumonia may be present in this group; more often the case is one of uncomplicated pleurisy. We had 2 such cases. Both showed no toxic cellular alterations, and the probability is that they were not pneumonic. There was also 1 case diagnosed "pneumonitis" with a degenerative index of 60%. It is more than likely that this patient had pneumonia with indefinite physical signs, since on the seventh day of her disease a sustained temperature of 103° F. dropped by crisis to normal and remained so.

Pleural Pneumonia Cases.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.	
R. P.	30	17.0	0	
J. S.	8	25.8	0	
E. C.	13	8.1	60	Diagnosed "pneumonitis."
M. C.	53	13.2–9.1	26	Pneumonia complicating pulmonary infarction.

Empyema. All cases showed toxic cytoplasmic changes in proportion to the degree of illness. One died with a mounting degenerative index which reached 62%; the other 3 cases recovered and their degenerative indices gradually dropped to zero with recovery.

Empyema Cases.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
J. M.*	2	33.4	62
J. G.	7	35.7–14.0	45–8
J. G.	2	21.8	20
J. Z.	4	32.7–14.9	50–11

* Died.

Fatal Cases in Pneumonia Group. There were 9 fatal cases: 7 of lobar and 2 of lobular pneumonia. In 8 of these the degenerative index ranged from 65% to 100%, averaging 82%. In the other, a proven case of lobar pneumonia in an aged male, the degenerative index was 17%. However, this patient lived in the hospital but 12 hours, only one examination was made and the smear was reported before examination as poorly stained.

Otitic Infections. Forty-seven cases of ear diseases were studied. Five cases of otitis media (Group A) and 17 cases of uncomplicated mastoiditis (Group B) showed no toxic cytoplasmic changes in the neutrophils, which finding paralleled mild clinical courses and uneventful convalescences. None of these 22 patients manifested any marked evidences of toxemia, sepsis or complications. Un-

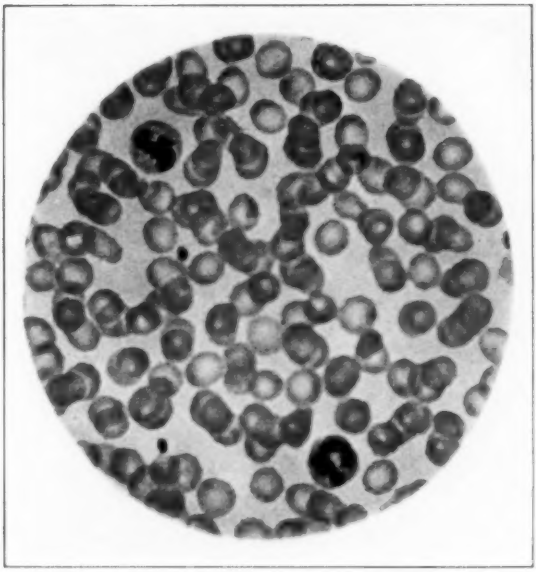

FIG. 1.—Blood smear showing cells without toxic granulations. Normal blood. (× 700.)

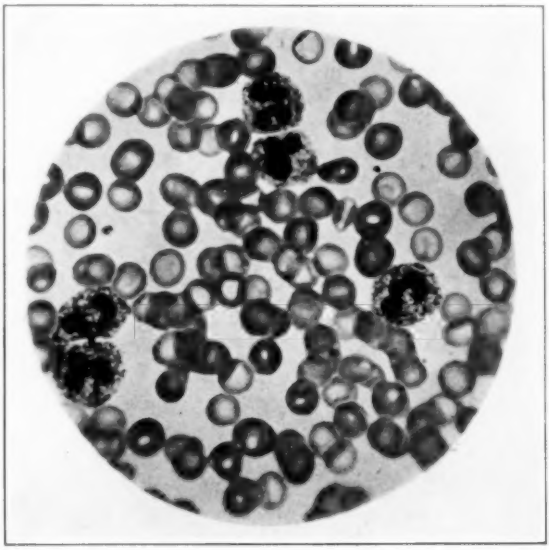

FIG. 2.—Blood smear showing cells with toxic granulations. From a case of lobar pneumonia. (× 700.)

eventful recoveries were never in doubt. The total leukocyte counts ranged from 15,000 to 28,000.

Group A Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
M. D.	4	19.9	0
E. G.	3	15.4–13.7	0
S. P.	18	16.3	0
S. P.	2	21.8	0
I. Z.	1	15.6– 6.1	0
Group B			
J. C.	10	18.2	0
P. S.	3	28.7	0
L. I.	6	16.5	0
S. I.	17	17.3	0
L. S.	7	23.8	0
P. S.	5	23.2–13.0	0
S. A.	1	15.2– 9.3	0
M. T.	46	10.9– 8.6	0
M. N.	2	19.4–16.4	0
M. A.	7	19.8	0
J. H.	6	20.9	0
L. W.	1	19.3	0
H. S.	7	25.7	0
B. S.	6	18.8	0
B. L.	4	15.6	0
M. B.	9	16.4	0
H. N.	11	12.8	0

In Group A the average stay in the hospital was 6 days. In Group B the diagnosis was confirmed by Roentgen ray examination and operation in 14 cases and by Roentgen ray examination in the remaining 3. The average period of hospitalization in this group was 11 days.

The remaining 25 cases evidenced toxic cytoplasmic changes varying from slight to a very intense nature. All had septic, stormy stays in the hospital and their degrees of illnesses were at all times comparable to the height of their degenerative indices. In some cases in which toxic changes occurred it was the first phenomenon to warn of the developing gravity of the condition. Of these 25 patients, 13 (Group C) developed diagnosable complications, namely, pneumonia, meningitis, erysipelas, adenitis, lateral sinus thrombosis, etc. As already shown by Group B, uncomplicated localized mastoiditis will not produce toxic cytoplasmic neutrophil changes; hence it can be stated that the toxic changes in this group were due entirely to the complications. As might have been anticipated, pneumonia produced the highest degenerative indices. Meningitis, it has been shown by others, does not produce these changes unless accompanied by bacteriemia. This observation was in accord with our findings in 2 cases, 1 with a complicating streptococcic meningitis yielding no toxic changes and the other with an otitic meningitis and a 25% degenerative index which could be ascribed to other factors. One case in this group, complicated

by erysipelas, demonstrated no toxic changes which we were unable to explain. The average period of hospitalization in this group was 48 days, which when compared to the 11-day period in Group B gives some idea of their illnesses.

Group C

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; complications.	
M. K.*	6	30.8	25	Otitic meningitis.
I. K.*	3	16.0– 6.2	5–91	Bronchopneumonia.
J. M.*	4	12.8–17.8	0	Streptococcic meningitis.
D. H.	3	22.3– 9.0	83–46	Lobar pneumonia.
W. H.	3	20.4–19.0	96–20	Lobar pneumonia.
F. B.	2	24.8–13.2	75–20	Erysipelas and adenitis.
C. G.	6	18.2–14.2	0	Erysipelas.
C. G.	7	23.3–13.9	28–11	Erysipelas and adenitis.
M. D.	7	13.8–11.4	0–35	Erysipelas.
D. G.	4	10.7– 6.6	23–24	Lateral sinus thrombosis.
I. S.	2	15.2–17.5	61–50	Lobar pneumonia.
E. W.	9	20.4–20.2	50–28	Lateral sinus thrombosis.
E. H.	36	9.1	41	Suppurative pansinusitis.

* Died.

Twelve cases of mastoiditis (Group D) showed toxic cytoplasmic changes. Whether these are the result of undiagnosed complications or very severe grades of mastoiditis we are unable to say. All had very septic courses with high degrees of morbidity; they were all quite as sick after mastoidectomy as before, and all gave their attending physicians grave concern. Their average length of morbidity was 19 days as compared to 11 days of Group B.

Group D

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
O. R.	4	28.2–15.5	42–18
J. L.	3	24.9–12.8	58– 5
R. W.	4	17.2– 7.2	26– 6
S. D.	3	15.9–10.6	45–28
M. B.	5	16.3–12.0	56– 0
E. H.	6	36.0–19.6	41–12
Y. R.	12	14.3	35
W. N.	5	24.2	31
J. G.	2	23.3–17.7	28–14
B. J.	3	22.7–20.3	92–65
S. P.	7	15.6–20.5	10–16
H. N.	2	40.5–23.3	13– 0

From these findings it should be expected that in dealing with uncomplicated otitis media or mastoiditis toxic cytoplasmic changes in the neutrophils should not be present. The addition of this finding to the hemogram should bring to mind the possibility of a complication or the spreading of what was until then a localized infection.

Illustrative Case. CASE 3.—T. C., male, aged 17 months, was admitted to the service of Dr. M. A. Weinstein, on January 31, 1934, for fever and discharge of pus from left ear. Temperature, 103° F.; pulse, 120; respirations, 40 per minute. Clinical diagnosis: acute otitis media. Roentgen

ray examination revealed chronic left mastoiditis. Blood count: Hemoglobin, 60%; erythrocytes, 3,400,000; leukocytes, 21,400; with 18 non-segmented and 58 segmented neutrophils, 18 lymphocytes and 6 monocytes. Degenerative index, 67%. The child was treated conservatively; the temperature reached 105° F. twice during the next week but only for a few hours each time. Clinically, improvement ensued and the discharge ceased. However, 2 additional leukocyte counts during this time were 21,450 and 15,200, respectively; the former showed an increase in the older neutrophils with a decrease in the younger forms, the latter with normal differential. But the degenerative indices for these counts were 81% and 70%. Nevertheless, because of clinical improvement, normal temperature, cessation of ear discharge and lowering of the total leukocyte count; in spite of the rising degenerative index the patient was discharged as improved. Within a few days he was readmitted (February 18) with a chill and temperature of 105° F. Total leukocyte count was 17,400 with 5 non-segmented and 63 segmented neutrophils, 25 lymphocytes and 7 monocytes. Degenerative index, 50%. Left mastoidectomy was performed; hemolytic streptococci recovered from mastoid cells. For a week following operation high temperature persisted; during the second week it ranged between 99° and 100° F. The total leukocyte counts dropped to normal but the degenerative indices were slower to reach zero. Patient was discharged on March 14 improved.

Upper Respiratory Infections. This term includes cases of acute "colds," coryza, tonsillitis, sinusitis, mild influenza and grippe. We found no toxic cytoplasmic changes in this group. When they occur in any of these conditions one should be ready to change or add to the diagnosis.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Range of degenerative index.
E. C.	5	16.3	0
F. G.	19	14.5	0
A. W.	22	11.9	0
I. N.	9	12.4	0

Tuberculosis. Many authors report the finding of mild toxic cytoplasmic changes in tuberculosis. However, early in the disease they are not present. They are more likely to occur in advanced cases in which the disease is making progress and in which secondary infection is a factor. Our cases were all early ones.

Patient.	Age.	Total leukocyte count, thousand per c.mm.	Percentage range of degenerative index.	
L. S.	55	11.4	0	
J. R.	41	9.3	0	
M. C.	31	16.1	0	
M. G.	57	12.7	7	Multiple skin infection.
M. M.	20	15.1	0	

Appendicitis and Peritonitis. Eleven cases of appendicitis were studied; 6 were acute suppurative in type; all were localized to the appendix. All began with an acute attack, mild fever and leukocytosis; all were promptly operated upon, and all had normal, rapid, uncomplicated recoveries. None of these showed toxic cyto-

plasmic changes. The other 5 were complicated, 3 with localized peritonitis and the formation of pelvic abscesses demonstrating degenerative indices ranging from 25% to 50%. The other 2 were instances of perforated appendicitis with generalized peritonitis. In them the degenerative indices ranged from 50% to 74% at the height of their diseases, and with recovery the cytoplasmic degenerative changes slowly disappeared.

Two additional cases of peritonitis of considerable interest present themselves. Both had fatal outcomes, the degenerative indices attesting to the gravity of the cases. In both this examination would have thrown light upon the diagnosis. One (S. G.) was under observation for possible meningitis, though peritonitis was considered. In meningitis these cytoplasmic changes do not occur to such a degree, hence the finding of so high a degenerative index (93%) would have favored a diagnosis of peritonitis. The other case (S. T.) was an obese middle-aged female, admitted for signs of intestinal obstruction thought to be due to the presence of a large pelvic tumor. The high degenerative index (91%) should have directed attention to peritonitis as the more likely abdominal condition.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.	
L. M.	18	14.2	0	Acute suppurative appendicitis.
F. K.	24	21.4	0	Acute suppurative appendicitis.
M. M.	31	15.8	0	Acute suppurative appendicitis.
B. C.	11	22.4	0	Acute suppurative appendicitis.
L. C.	17	15.2	0	Acute suppurative appendicitis.
M. M.	20	25.4	0	Acute suppurative appendicitis.
D. M.	17	15.2	20	Acute suppurative appendicitis, with localized peritonitis and pelvic abscess.
H. S.	22	16.0	33–15	Acute suppurative appendicitis, with localized peritonitis and pelvic abscess.
M. K.	9	20.1	50–20	Acute suppurative appendicitis, with localized peritonitis and pelvic abscess.
A. W.	14	15.2	74– 0	Perforative appendicitis with generalized peritonitis.
S. A.	25	25.9	50– 0	Perforative appendicitis with generalized peritonitis.
S. G.	1	19.9	93	Primary streptococcic peritonitis.
S. T.	51	14.9	91	Generalized peritonitis secondary to gangrene of bowel due to embolism of mesenteric artery.

Illustrative Case. Case 4.—A. W., male, aged 14, was admitted to the service of Dr. B. Lipschutz, on February 15, 1934, for pain in right lower abdominal quadrant of 2 days' duration accompanied with nausea and vomiting. Temperature, 105° F.; pulse, 160; respirations, 34 per minute. Clinical diagnosis: acute perforated appendicitis with peritonitis. Blood count: Hemoglobin, 82%; erythrocytes, 4,200,000; leukocytes, 15,200; with 34 non-segmented and 58 segmented neutrophils, 8 lymphocytes. Degenerative index, 6%. Ruptured appendix was removed and peritoneal

cavity drained on day of admission. In spite of general supportive measures, including blood transfusions for sepsis, the temperature remained elevated and vomiting persisted. Total leukocyte count was now 21,700 with 15 non-segmented and 75 segmented neutrophils, and the degenerative index had risen to 74%. Additional drainage was instituted on February 22 without improvement. For the next 2 days condition was grave, the total leukocyte counts and differentials remaining the same with slight variation and the degenerative index persisted at 70%. Cecostomy was done on February 24 for obstruction, and drainage now became profuse. On March 5, there was the first evidence by temperature chart that the patient was improving; the total leukocyte count was 16,400 with 40 non-segmented and 46 segmented neutrophils and a drop in degenerative index to 40%. On March 13, improvement continuing, degenerative index was 26%. On March 17, total leukocyte count was 14,200, differential nearly normal and degenerative index 4%. On March 29, total leukocytes, 6050; degenerative index, 0%. He was discharged on April 1 as cured.

Biliary Tract Disease. Localized infections of the liver or bile ducts yield, as a rule, no toxic cytoplasmic changes, as can be illustrated by these 7 cases. With an added complicating factor the degenerative index will rise.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.	
H. R.*	33	28.4–19.2	70–53	Subhepatic abscess with peritonitis following cholecystectomy.
L. S.*	65	23.4	0	Choledocholithiasis with cholemia and liver atrophy.
B. S.	78	11.8	5–29	Acute cholecystitis.
S. G.	6	15.5	0	Acute hepatitis
E. K.	3	13.7	0	Acute hepatitis.
A. R.	70	16.9	0	Choledocholithiasis.
R. S.	33	20.8	0	Subacute cholecystitis.

* Died.

Miscellaneous Suppurations. In this group of 21 cases of suppurations in various parts of the body the same rule holds true, namely, that in a localized infection in which but little absorptive surface is exposed to the infecting agent we find no cytoplasmic pathologic changes. However, in spreading infections toxic changes begin to appear in proportion to the severity and extent of the disease. Retropharyngeal abscesses yield high degenerative indices. Subpectoral abscesses with their large absorptive areas showed high degrees of pathologic cytoplasmic changes. Uncomplicated salpingitis produced no toxic neutrophilic changes, but when complicated by suppurations in the uterus, septicemia or pelvic abscesses with peritonitis, then toxic cytoplasmic changes begin to mount in degree corresponding to the extent of the surface attacked. In the 2 cases of perinephric abscesses, 1 was well localized and unassociated with toxic changes. The other was more extensive with greater invasion of perinephric spaces, and here we found 10% of the neutrophils toxic. Had operation not been performed at this

point there is no doubt that the degenerative index would have risen. Carbuncles show high toxic changes in contrast to suppurative adenitis which rarely yield such findings. Cellulitis, when slight, yields only mild toxic changes but, when spreading and associated with suppuration, the degenerative index may reach 100% and the outcome become increasingly grave. Pyelitis, with no further kidney damage and if draining, yields no toxic cytoplasmic changes.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index: diagnosis.	
P. N.	7	24.5	56	Retropharyngeal abscess.
G. G.	4	21.5	42	Retropharyngeal abscess.
L. L.	5	21.4	63	Retropharyngeal abscess.
H. R.	30	14.2	70	Spreading subpectoral abscess.
P. S.	18	20.0	46	Spreading subpectoral abscess.
R. L.	29	22.6	0	Bilateral salpingitis.
R. M.	26	24.8	0	Bilateral salpingitis.
M. B.	35	10.5	28	Suppurative metritis.
I. G.	21	19.2	64	Septic abortion with septicemia.
H. M.	31	21.0	38	Suppurative metritis.
M. G.	26	18.8	66	Bilateral tuboövarian abscesses with pelvic peritonitis.
N. P.	54	16.5	0	Perinephric abscess.
H. L.	23	14.7	10	Perinephric abscess.
M. C.	42	16.2	5	Cellulitis of hand, localized.
S. L.	38	24.8	89	Spreading cellulitis with suppuration.
M. G.	42	17.2	32	Spreading carbuncle of neck.
M. L.	22	17.8	18	Inguinal abscess.
E. G.	18	20.6	0	Axillary abscess.
E. S.	9	22.4	0	Axillary abscess.
E. O.	32	30.4	0	Perirectal abscess.
B. G.	5	20.4	0	Pyelitis.

These examinations represent the height of the disease.

Osteomyelitis. This group of cases illustrates how an increasing degenerative index can warn the clinician of the seriousness of the outcome or predict a favorable prognosis when its steady decrease accompanies the clinical course. S. L. on admission showed no toxic cytoplasmic changes. Soon these developed and increased rapidly with each examination of the blood, finally reaching 100%, and the patient expired. C. S. on admission had a degenerative index of 83%, which after the institution of treatment gradually dropped from day to day until cure was established and the index reached zero. The other cases illustrate that acute fulminating osteomyelitis show high degrees of toxic cytoplasmic changes, whereas the chronic type demonstrates much different findings.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.	
S. L.*	10	14.6–12.6	0–100	With septicemia.
R. P.*	11	13.2	47	With septicemia.
I. L.	58	19.2	67	
C. S.	60	25.4–10.4	83– 0	
V. H.	7	8.9	22	
D. R.	13	8.4	0	

* Died.

Illustrative Cases. CASE 5.—S. L., female child, aged 10, was admitted to the service of Dr. M. B. Cooperman, on March 2, 1934. Following mild sore throat of 2 days' duration she developed fever with pain and tenderness in the region of the right tibial tubercle. Temperature was 105° F.; pulse, 130; respirations, 26 per minute. Clinical diagnosis: acute osteomyelitis of hematogenous origin. Blood count: Hemoglobin, 76%; erythrocytes, 3,560,000; leukocytes, 14,600; with 4 non-segmented and 78 segmented neutrophils, 8 lymphocytes and 10 monocytes. Degenerative index, 0%. Blood chemistry and serology normal; blood culture sterile in 48 hours. Roentgen ray examination negative for acute osteomyelitis. Right tibia was drilled, pus located and drained. Blood transfusion and supportive measures were instituted. On March 6, child was septic and the temperature had assumed pump-handle type. Total leukocytes were 12,900, with 47 non-segmented and 30 segmented neutrophils. Degenerative index, 40%. Right knee was aspirated, considerable pus removed; organism, Staphylococcus aureus hemolyticus. Repeated blood culture now returned positive for the same organism as found in knee. Patient steadily went downhill in spite of all measures of treatment. By serial counts it was interesting to note how accurately the progress was followed by the mounting degenerative index. On March 7, total leukocytes, 11,000; 40 non-segmented and 32 segmented neutrophils; degenerative index, 58%. On March 9, total leukocytes, 21,000, with 22 non-segmented and 50 segmented neutrophils; degenerative index, 72%. March 12, total leukocytes, 33,400; 31 non-segmented and 52 segmented neutrophils; degenerative index, 80%. March 14, total leukocytes, 18,800; 35 non-segmented and 38 segmented neutrophils; degenerative index, 96%. March 16, the day on which the patient expired, the total leukocytes were 12,600, with 28 non-segmented and 58 segmented neutrophils, and the degenerative index 100%.

In Contrast. CASE 6.—C. S., male, aged 60, was admitted to the service of Dr. B. Lipschutz, on January 30, 1934, for pain and swelling of the right thigh with fever. Temperature, 103.8° F.; pulse, 130; respirations, 22 per minute. Blood chemistry and serology normal. Repeated blood cultures sterile. Blood count: Hemoglobin, 62%; erythrocytes, 3,200,000; leukocytes, 25,400, with 26 non-segmented and 68 segmented neutrophils, 5 lymphocytes, 1 monocyte. Degenerative index, 83%. Roentgen ray examination: acute periostitis. Incision and drainage of the right femur, pus found, and drained. Culture from femur: non-hemolytic streptococci. Blood transfusions and general measures to combat sepsis instituted. February 7, condition still septic; total leukocytes, 14,000, with 18 non-segmented and 74 segmented neutrophils. Degenerative index, 74%. On February 11, the temperature showed some evidence of striking a lower level and clinical improvement was apparent. Total leukocytes, 13,200, with 24 non-segmented and 64 segmented neutrophils; degenerative index, 45%. On February 19, the temperature was normal, general condition good, total leukocytes, 10,400, with 17 non-segmented and 65 segmented neutrophils; degenerative index, 26%. On February 23, the total leukocytes were 10,400, with 14 non-segmented and 54 segmented neutrophils; degenerative index, 0%. He was discharged on February 25 as cured.

Meningitis. There are 6 cases in this series, 5 were fatal, 1 recovered. As pointed out by Naegeli, marked toxic cytoplasmic changes in this disease are usually absent unless bacteriemia be present. In 1 case (B. C.) accompanied by a positive blood culture the degenerative index reached 76%. The others manifested slight or no toxic changes.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.
B. C.*	2	17.5	76 Meningococcic meningitis with meningococcemia.
R. S.*	4	11.8	10 Otitic meningitis.
J. R.*	23	13.8	10 Pneumococcic meningitis.
J. M.*	4	17.8	0 Streptococcic meningitis.
M. K.*	6	30.8	25 Otitic meningitis.
T. P.	1	16.8–9.8	20 Meningococcic meningitis.

* Died.

Erysipelas. Most investigators have found toxic cytoplasmic changes in erysipelas. Two of our cases with adenitis showed these changes and 2 did not.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
P. D.	2	14.0	0
C. G.	6	18.2	0
C. G.	4	23.3–13.9	26–11 With adenitis.
F. B.	2	24.8–13.8	75–20 With adenitis.

Ulcerative Colitis. This disease usually presents mild toxic cytoplasmic changes in the neutrophils throughout its course. With increasing gravity of the case, and as the patient becomes more septic, the cellular cytoplasmic changes are intensified until a degenerative index of 100% may be reached in the advanced cachectic state. The patient who died (B. G.) demonstrated a gradually increasing degenerative index over a period of months until it reached 91% before death.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
B. G.*	16	10.0–21.4	0–91
B. B.	26	15.3	18

* Died.

Body Burns. Burns, as a rule, produce no cytoplasmic neutrophil changes. However, when infection with large area for absorption is present these changes occur. In our fatal case (L. B.), the patient was hospitalized for more than 400 days, in the last few months the degenerative index steadily mounting and remaining at 100% for a few weeks before death.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index.
L. B.*	7	21.0–15.0	75–100 Secondary infection.
M. P.	9	20.0–18.0	0– 35 Secondary infection.
M. R.	10	15.0	0 Localized, uninfected.

* Died.

Neoplastic Diseases. Of these 11 cases of tumors, 6 presented no toxic cytoplasmic changes. These included 4 cases of carcinoma with and without metastasis, 1 case of Hodgkin's disease and 1 case

of non-malignant ovarian cyst. Hence, benign tumors, malignant tumors, metastasis or even fatality in this group are not causes for these changes. Five cases did demonstrate toxic cytoplasmic alterations, the degenerative indices ranging from 30% to 87%. Each of these 5 was complicated by infection, and it is highly probable that the toxic cytoplasmic changes in the neutrophils was due to the infection rather than to the neoplasm. In each case the degree of the changes paralleled the intensity of the infection. As mentioned before, 3 cases were fatal, but the degenerative index could not be used as a measure of prognosis in these cases. Barta has found toxic changes in cases of uncomplicated malignancy. We have not been able to confirm his finding.

Patient	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.	
M. K.*	66	69.0–59.7	72–87	Carcinoma of stomach with metastasis; huge rectal and pararectal abscess.
P. B.*	56	18.6–18.0	0	Carcinoma of stomach and pancreas.
S. S.*	49	5.0	44	Carcinoma of colon; wound infection and necrosis.
S. T.	54	14.2	0	Carcinoma of stomach with metastasis.
R. K.	28	6.5	0	Carcinoma of bronchus.
H. S.	45	17.3	30	Carcinoma of breast; massive wound infection with necrosis.
A. S.	48	13.9	50	Spongioblastoma of brain; suppurative pansinusitis.
S. T.	67	12.5	0	Carcinoma of stomach.
J. M.	56	18.6–7.8	35–0	Abdominal carcinomatosis.
R. Z.	40	17.2	0	Non-malignant ovarian cyst.
F. C.	58	16.5	0	Hodgkin's disease.

* Died.

Cardiovascular Disease. This series was taken as a control group. Most of these cases had non-infectious degenerative lesions of the cardiovascular system. They are compared with our groups of infectious diseases. Most of them were very ill; many were in critical condition. The acute rheumatic types were clinically active. Yet none manifested any toxic cytoplasmic neutrophil alterations. One case of coronary thrombosis yielded a degenerative index of 30%, but it was found to be due to an apical pneumonia complicating the picture. Hence, we can definitely state, no matter how ill the cardiac patient, one should not expect to find toxic changes unless secondary infection is superimposed.

Patient	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.	
A. A.*	50	13.2	0	Hypertensive C. V. disease with decompensation.
H. F.*	65	12.8	0	Hypertensive C. V. disease with decompensation.

Patient	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.	
B. L.*	50	17.5	0	Luetic C. V. disease with decompensation.
R. W.*	70	28.4	0	Arteriosclerotic C. V. disease with decompensation.
H. L.	59	19.3	0	Luetic C. V. disease with hypertension.
E. W.*	60	12.8	0	Hypertensive C. V. disease with decompensation.
E. C.	73	20.7	0	Arteriosclerotic C. V. disease with cerebral thrombosis.
R. M.	68	16.5	0	Arteriosclerotic C. V. disease.
B. P.	24	13.2	0	Rheumatic endocarditis.
D. M.	60	14.9	30	Coronary thrombosis; apical pneumonia.
S. B.	59	13.9	0	Coronary thrombosis.
J. B.	47	19.2	0	Hypertensive C. V. disease.
J. G.	19	17.6	0	Rheumatic endocarditis.
R. R.	37	15.4	0	Rheumatic pancarditis.
J. Z.	32	17.7	0	Rheumatic pancarditis with polyarthritis.
G. K.	7	16.2	0	Recurrent rheumatic endocarditis.

* Died.

Pregnancy. Fifteen cases of pregnancy were studied. Many observers have reported toxic cytoplasmic changes in ruptured ectopic gestation and account for it by absorption. Whatever the explanation, our 2 cases also demonstrated this finding. Of the 7 with normal pregnancies, deliveries and puerpera, none showed any degenerative cytoplasmic alterations. The other 6 cases showed toxic cytoplasmic changes in the neutrophils, of which 5 could be attributed to septic complications in the puerperium. One case with a degenerative index of 31% manifested no complication and we were unable to explain it.

Therefore, we would conclude that in normal pregnancy without morbidity no toxic alterations in the neutrophils should occur. Their presence means definite complication by infection.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.	
M. M.	25	27.0–10.2	76–9	Ruptured ectopic gestation.
E. McG.	27	19.9–9.3	31–0	Ruptured ectopic gestation.
P. R.	32	7.8	0	Normal pregnancy.
G. Z.	19	13.3	0	Normal pregnancy.
S. S.	21	10.9	0	Normal pregnancy.
F. D.	26	10.6	0	Normal pregnancy.
A. S.	22	16.2	0	Normal pregnancy.
F. B.	28	26.0	0	Normal pregnancy.
A. S.	33	17.4	0	Normal pregnancy.
R. S.	25	29.5–14.9	59–11	Puerperal infection.
M. M.	27	25.8–14.7	23–59	Puerperal infection.
L. S.	28	19.4–12.2	25–75	Puerperal infection.
R. Z.	31	22.0–11.2	40–65	Puerperal infection.
M. P.	24	20.0–12.4	31–38	Puerperal infection.
D. F.	24	19.3–12.7	6–31	Normal pregnancy.

Arthritis. Search for toxic cytoplasmic changes in the neutrophils in various forms of arthritis proved vain. Regardless of the intensity of the illness these changes are absent. The only instance in which they may be found is when a positive blood culture is present in the infectious, rheumatic or gonorrheal types.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.
D. S.	49	25.0	0 Polyarthritis.
R. W.	23	23.3	0 Gonorrheal arthritis.
R. McK.	5	17.9	0 Suppurative arthritis.
S. S.	39	16.9	0 Infectious arthritis.
J. Z.	32	17.7	0 Rheumatic arthritis.

Renal Disease. Toxic cytoplasmic changes are not found in the neutrophils in nephritis either of the degenerative or inflammatory types—even fatal cases present no such findings.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.
F. R.*	54	8.6	0 Chronic diffuse glomerular nephritis with hypertension.
F. F.	26	8.8	0 Acute diffuse glomerular nephritis.
J. J.	5	13.7	0 Focal hemorrhagic nephritis.
I. P.	4	13.9	0 Focal hemorrhagic nephritis.

* Died.

Miscellaneous. This series represents a miscellaneous group of cases non-infectious in origin all of which presented no toxic cytoplasmic changes in the peripheral neutrophils unless complicated by infection. It is of value as an additional control for comparative purposes.

Patient.	Age.	Total leukocyte count, thousands per c.mm.	Percentage range of degenerative index; diagnosis.
D. P.*	3	14.3	0 Hydrocephalus.
M. K.	40	17.5	0 Bronchial asthma.
L. S.	57	16.6	0 Bleeding peptic ulcer.
M. S.	24	20.2	0 Strangulated hernia.
H. R.	65	12.8	0 Hemorrhoids.
A. V.	60	15.9	0 Hypertrophied prostate.
M. R.	51	19.4	0 Fissure in ano.
W. P.	16	12.4	0 Fracture.
O. R.	28	12.0	0 Pilonidal cyst.
R. F.	31	6.2	0 Typhoid fever.
M. G.	62	19.4	0 Diabetes with gangrene.
E. S.	65	18.3–15.7	42 Hypertrophied prostate; abscess of leg.
H. S.	54	19.2	0 Acute leukemia.

* Died.

Summary. The subject of toxic cytoplasmic alterations in peripheral neutrophils is presented with a discussion of the conditions in which these changes occur and those in which they are not found.

These findings have been shown to be of value diagnostically. They are most uniformly found in infections, and probably their greatest value lies in differentiating localized from generalized infections or the development of complications, whether this be a secondary infection or a spread of the initial infection. These changes are most uniformly found in pneumonia, peritonitis, bacteriemias and septicemias. The addition of toxic cytoplasmic changes in the neutrophils to the hemogram in which they were previously absent should warn the attending physician of an added complication.

From a prognostic viewpoint, an increasing degenerative index lends increasing gravity to the outcome.

The addition of this examination as a routine to the hemogram is of clinical value, often gives more information than the total leukocyte count and if followed serially is often more informative than the Arneth-Schilling shift.

No hemogram in infection or in serious disease states is complete without the determination of toxic cytoplasmic changes and their recording in some quantitative scheme, such as Rosenthal's "degenerative index."

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MECHANISMS OF CARDIAC RHYTHM.

ILLUSTRATED BY UNUSUAL HUMAN ELECTROCARDIOGRAMS.

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THE purpose of this paper is to present unusual electrocardiograms, which elucidate the generally accepted principles of cardiac rhythm. Lewis[1] has stated as a law "that if several heart centers are simultaneously active, the heart as a whole will be dominated by the center which develops its rhythmic impulse most rapidly." This is true if the reservation is made that conduction both forward and retrograde is unimpaired.

In the normal mechanism, the heart is controlled by the sino-auricular node because its rate of impulse formation exceeds that of the lower rhythm centers, namely, the auriculoventricular node and idioventricular centers. When the conducting mechanism is such that conduction forward (auricle to ventricle) and retrograde (ventricle to auricle) is unimpaired, sino-auricular control can be replaced by artificial stimuli, provided the rate of these stimuli exceeds that of the sinus node.[2] The excitation wave will spread from the site of stimulation through auricles and ventricles, and the entire heart will respond to the new center. When the auricle is stimulated the normal sequence of contraction continues. When the ventricle is stimulated, the sequence is reversed; the ventricle contracts before the auricle and the impulse is conducted backward.

The mechanism of cardiac rhythm is modified by variations in the state of conduction between auricle and ventricle. Four possible states may be considered; (1) The conducting tissue may transmit impulses in either direction (forward and retrograde conduction equal); (2) the conducting tissue may convey impulses from auricle to ventricle only (unidirectional block[3]); (3) only retrograde impulses are transmitted; (4) both forward and retrograde conduction may be impaired or blocked (complete heart block).

The rhythms and spread of excitation when forward and retrograde conduction are equal has already been considered. In the second condition, unidirectional (retrograde) block, impulses originating in the auricle will reach the ventricle; but none beginning in the ventricle will be conducted to the auricle. The normal sequence of the cardiac cycle continue provided the auricular center is the most rapid. Should the rate of a ventricular center exceed that of the auricle, however, the two chambers will beat independently. The rapid ventricular stimuli control the ventricle because they submerge the slower impulses conducted from the auricle. Impaired retrograde conduction blocks the rapid impulses from the

ventricle and the auricle responds independently to the rhythm of its own slower pacemaker. The ventricular rate in such a case exceeds the auricular.

The third possibility, forward block[3] alone is a rare condition. It is the reverse of the preceding mechanism. Here rhythm control of the entire heart is possible when the most rapid center is in the ventricle and dissociation exists when the auricular center exceeds the ventricular center.

In the fourth condition, we have the common clinical entity of complete heart block. The rhythm and rate of each chamber may be slow or rapid. The auricular rhythm may vary as widely as that of a sinus bradycardia to that of auricular fibrillation. The ventricular rate may vary from the usual slow rate of the idioventricular center to that of paroxysmal ventricular tachycardia or ventricular fibrillation. Usually the auricles beat more rapidly than the ventricles; but in rare instances this relationship may be reversed.

The above principles of the cardiac mechanisms limit the number of possible rhythms as follows:

I. Unidirectional Block (Retrograde): This is probably the normal state of conducting tissue.
- A. *Most rapid center in auricle.*
  1. Normal sinus rhythm.
  2. A–V nodal rhythm.
     - (*a*) Escaped beat
     - (*b*) Escaped rhythm

     } When sinus node is depressed.
     - (*c*) Premature beat
     - (*d*) Nodal tachycardia

     } When A–V nodal center is stimulated.
  3. Ectopic auricular rhythm.
     - (*a*) Premature auricular contraction.
     - (*b*) Auricular ectopic tachycardia.
  4. Auricular flutter.
  5. Auricular fibrillation.
- B. *Most rapid center in ventricle*—Ventricle alone responds; auricle responds to its own center.
  1. Isolated escaped ventricular beat
  2. Escaped ventricular rhythm

  } When sinus node is depressed.
  3. Premature ventricular contraction
  4. Ventricular tachycardia
  5. Ventricular fibrillation

  } When ectopic center is stimulated.
  6. Parasystole.

II. Bidirectional Conduction—Forward and Retrograde: (Rare).
- A. *Most rapid center in auricle*—The rhythms are the same as Ia.
- B. *Most rapid center in ventricle*—Entire heart responds and sequence of contraction is reversed. The rhythms are same as Ib. Parasystoles of auricular origin cannot occur.

III. Complete Heart Block—Both chambers are always independent.
- A. Auricular rhythms—as under Ia.
- B. Ventricular rhythms.
  1. Idioventricular rhythm (origin above bifurcation of bundle tissue).
  2. Ectopic ventricular rhythm (origin below bifurcation of bundle tissue).
  3. Ventricular tachycardia.
  4. Ventricular fibrillation.

IV. Unidirectional Block—Forward—(Very rare).
A. *Most rapid center in auricle*—Auricle alone responds; ventricle responds to its own center—Rhythms are the same as Ia.
B. *Most rapid center in ventricle*—Both chambers respond—Sequence of contraction reversed—Rhythms are the same as IIIb.

In the extensive literature on arrhythmias, the material appears in the main as individual case reports illustrating one or other of these mechanisms. Lewis[8] includes examples of the great majority of the possible mechanisms, some of which were obtained experimentally on animals. He does not treat them collectively but discusses each as it serves to illustrate one or other phase of the subject. It seemed useful therefore to review the subject of arrhythmias using clinical electrocardiograms only.

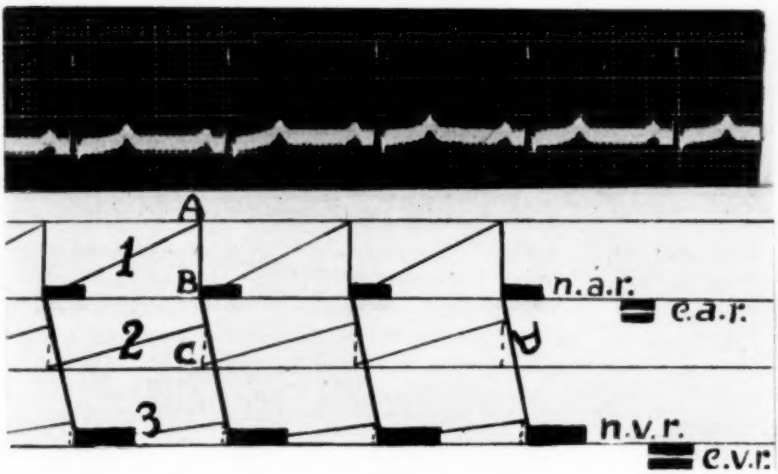

Fig. 1.—Normal sinus rhythm.

To facilitate in the discussion of the electrocardiograms a uniform graphic illustration of the mechanism is included under each figure. The general scheme is shown in Figure 1 which diagrammatically illustrates the mechanism in normal sinus rhythm. Lines 1, 2, and 3, represent impulse formation in the three rhythmic centers—the sinoauricular, auriculoventricular and ventricular centers respectively. It is assumed that the three centers are building stimuli simultaneously. Horizontal lines A, B, and C, represent the height to which these impulses must be raised before they attain effectiveness. The sinoauricular node is represented as developing stimuli most rapidly. The auricular response is represented by the solid upper rectangle (n.a.r.). The line D, joining the two rectangles represents the duration of excitation in the auricle and of conduction to the ventricle.*

* This is not entirely true to fact insofar as the string does not deflect until a sufficient mass of muscle has been activated.

The lower rectangle (n.v.r.) represents a normal ventricular response. As the excitation wave spreads over the two lower centers it discharges the impulses forming in them before they have reached effectiveness.[1] The width of the rectangle represents the refractory period. In succeeding electrocardiograms impulse formation in an ectopic center will be represented by an ascending broken line. Ectopic auricular and ventricular responses will be shown by horizontal bars below the second (e.a.r.) and lowest lines (e.v.r.) respectively.

The illustrations that follow will be presented along the plan of the outline. Figures 2 to 10 show rhythms occurring when the conducting tissue is normal and is capable of transmitting impulses from auricle to ventricle, but not from ventricle to auricle. (Unidirectional retrograde block), Group I.

Figure 2 illustrates isolated *A–V* nodal escape—when the sinus is depressed by pressure over the eyeball. (In the Table 1 A 2*a*). When the sinus node is sufficiently slowed, as occurs after the second cycle, a complex arising from an *A–V* nodal center appears. No inverted auricular complexes are seen and it must be assumed that the impulse is not conducted from the lower center and that retrograde conduction is blocked. There is a long period of cardiac standstill. This would indicate that the *A–V* node as well as the *S–A* node were depressed—but that the *A–V* node recovered first. Another intrepretation might be that the *S–A* node alone was depressed and that the gradual quickening of the *A–V* nodal rhythm represents "rhythm of development."[4] Toward the end of the figure the sinus node recovers from vagus influence and resumes cardiac control.

Figure 3 illustrates escape of an ectopic ventricular center (Group IB 1.) The isolated ectopic ventricular beats shown are not succeeded by an abnormal auricular complex indicating that the impulses from the ventricle are not conducted backward. The ventricular complex is abnormal and appears consistently whenever the *S–A* node is slowed to a cycle length of 1.3 seconds. This was true for a long strip of electrocardiogram in which many escaped beats appeared. It is of interest to point out that the *R–R* intervals preceding ectopic beats are always equal. This seems to indicate that the slow ectopic center is continuously active but is submerged by the slightly more rapid auricular pacemaker. When the latter slows sufficiently the submerged center develops an effective stimulus and escapes from auricular control. Here as in the previous example the depressant factor seems to act only or predominantly upon the sinus node—allowing for escape of lower centers.

The preceding electrocardiograms are examples of isolated escaped beats of a lower center when the sinus is depressed. This mechanism is considerably less common than that in which the rate of the sinus remains unchanged while a dormant rapid center

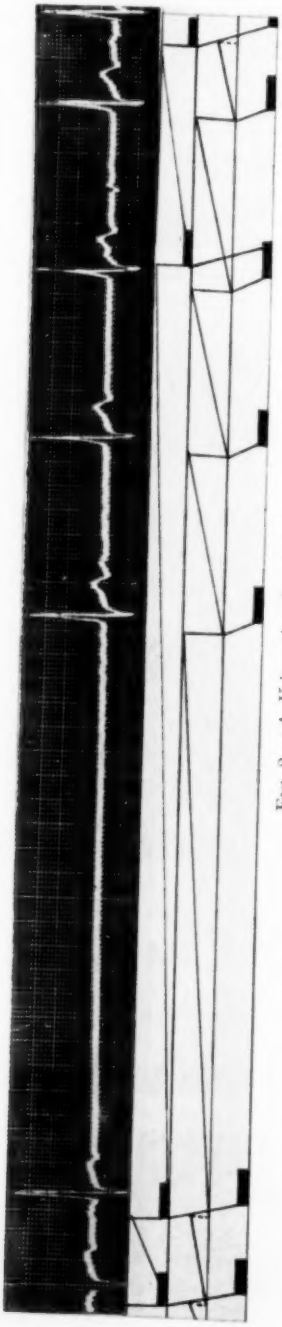

FIG. 2.—A-V junctional escape.

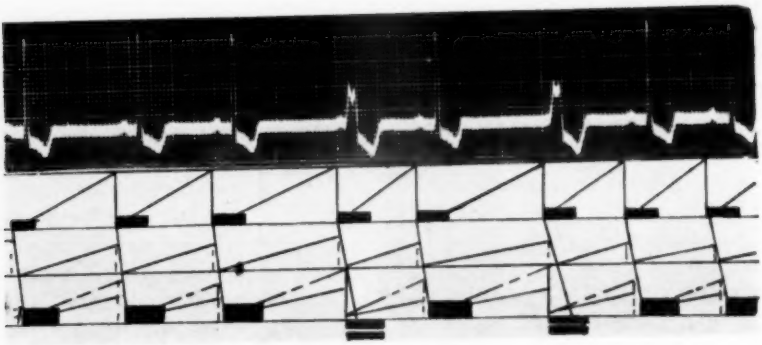

FIG. 3.—Ectopic ventricular escape.

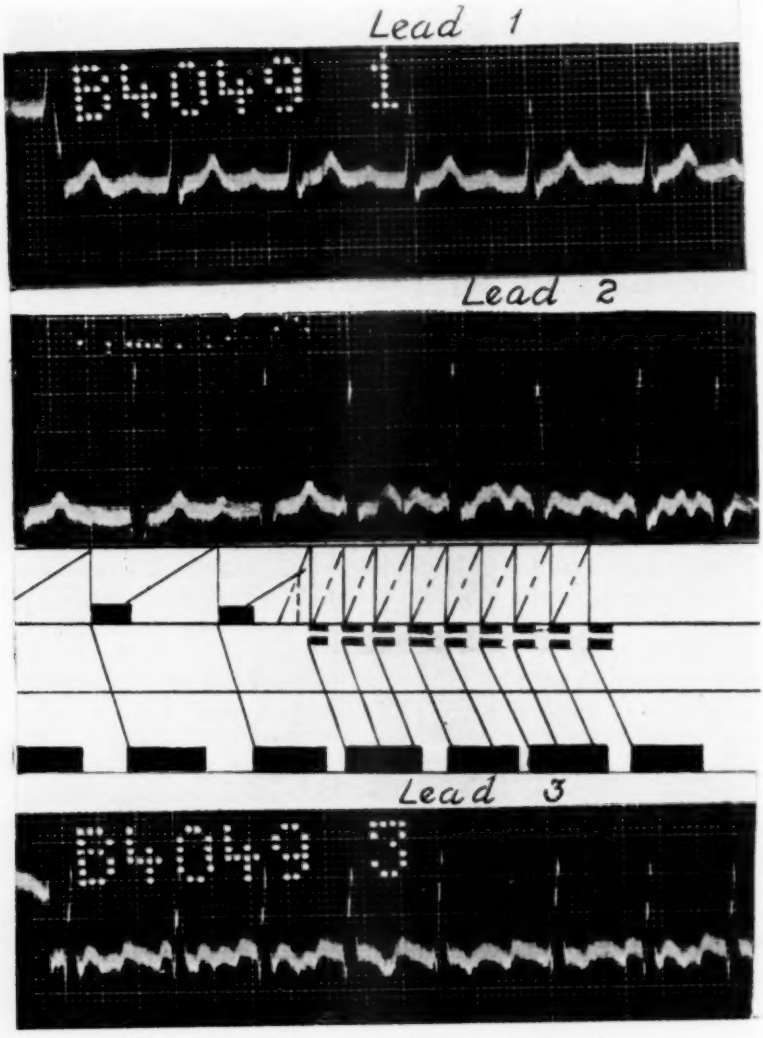

FIG. 4.—Transition from sinus rhythm to auricular flutter.

is stimulated to activity. Premature contractions and the various tachycardias are familiar examples. Most common are the rhythms originating in the auricle—auricular premature contractions, and the various auricular tachycardias. These are too familiar to need repetition. One interesting case of this type will be shown because the electrocardiogram shows a transition from one rhythm to another.

Figure 4 illustrates dormant flutter rhythm spontaneously stimulated to activity (Group 1A 4). The transition appears in Lead II. This case is included in the group of unidirectional retrograde block because of the following reasons: The flutter cycle lengths are 0.21 second. This would indicate that the auricular refractory period is equal to or less than 0.21 second. During sinus rhythm the *P–R* interval is 0.24 second. Ventricular excitation begins, therefore, 0.03 second after the auricle has passed out of its refractory period.

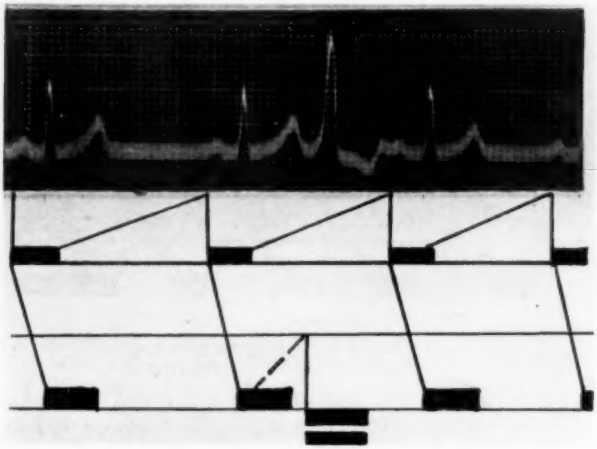

FIG. 5.—Premature ventricular contraction (interpolated).

If the ventricular impulse were conducted to the auricle it would reënter that chamber after its refractory period and elicit an auricular response—"reciprocal beat."[3] To explain the absence of retrograde auricular response it must be assumed that the impulses are blocked and that retrograde conduction is impaired.

Rapid dormant centers of the ventricle are rarely stimulated to continuous activity though they frequently dominate isolated cardiac cycles—premature ventricular contractions are familiar examples, and need no illustrations. It is worth pointing out, however, that when a ventricular premature beat appears it is extremely rare to see it followed by a retrograde auricular response. This is

not because the retrograde impulse reaches a refractory auricle, for when a premature ventricular contraction appears very early in diastole, such as occurs when the beat is interpolated, the auricle still continues to respond to its own center. This indicates that normally retrograde conduction is impaired. Figure 5 shows an interpolated ventricular premature contraction and demonstrates that phenomenon. Premature ventricular excitation occurs when the auricle is out of its refractory phase—but no retrograde auricular response follows. It must be assumed that the ventricular impulses are blocked and the retrograde conduction is impaired. This arrhythmia fits into Group Ib 3.

Figures 6 to 9 are rare arrhythmias—showing continuous activity of low rapid centers.

In all of these the conducting mechanism fits into the classification of unidirectional block with retrograde conduction impaired (Group I).

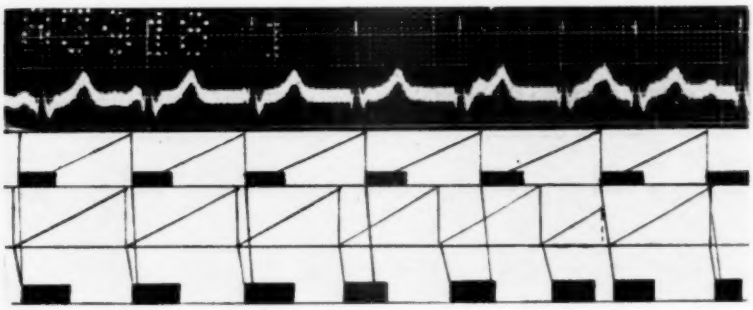

FIG. 6.—Independent rhythm with retrograde block. Auricle controlled by sinus node; ventricle controlled by *A–V* node.

Figure 6 is a paroxysm of rapid rhythm, either of the *A–V* nodal or idioventricular centers (Group Ia 2*d*). The auricles and ventricles are controlled by independent centers, the auricle by the sinus node, the ventricle by the lower center. This type of arrhythmia has appeared in the literature as complete heart block.[5] This is a mistaken interpretation because the conducting mechanism is normal. It will be noted that the ventricular rate is slightly higher than the auricular, the ventricular cycle length is 0.66, and the auricular cycle length is 0.70 second. The evidence against complete heart block and in favor of normal auriculoventricular conduction is revealed by complex 7. This complex is in response to a supraventricular impulse and appears as a premature beat succeeding an auricular complex which superimposes the *T* wave. In the entire curve wherever this relationship of *P* and *T* existed the succeeding ventricular complex was premature (parasystole).[6] This premature beat represents a response to a normally conducted sinus stimulus which reached

the ventricle after it had passed out of its refractory state. Succeeding sinus impulses, however, are anticipated by those from the more rapid *A–V* node which again takes up the rhythm of the ventricle. This continues until another sinus stimulus opportunely placed elicits a ventricular response. The two independent rhythms continue with periodic sinus control of both chambers. This can be possible only if conduction from auricle to ventricle is intact and retrograde conduction impaired.

Figure 7 is another example of the same mechanism and illustrates the conditions in most of the ventricular tachycardias (Group Ib 4). The center controlling the ventricle is below the bifurcation of the conducting tissue. It displaces the slower impulses from the auricle and controls the ventricle. The rapid impulses are not conducted backward to the auricle which continues to respond to the slower sinus node. It will be noted that after the second and

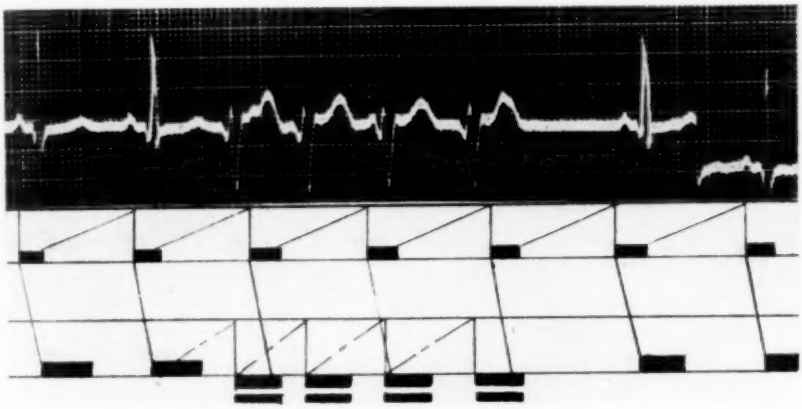

Fig. 7.—Ventricular rhythm with retrograde block.

possibly also after the third ectopic beat a retrograde impulse would have reached the auricle considerably after its excitation phase and most probably after its refractory period. It is difficult to explain the absence of a retrograde auricular response on the basis that the retrograde impulse falls on a refractory auricle. One must rely on the explanation that the ventricular impulses are not conducted to the auricle and that retrograde block exists.

Arrhythmias of the same type are illustrated in Figs. 8 and 9. The former was produced by pressure over the precordium.[7] That in Fig. 8 occurred spontaneously. They are present as additional examples of Group Ib 4 because of their unusual interest. In both arrhythmias sinus control of the ventricle is replaced by a more rapid center probably very near the bifurcation of the His bundle. These impulses are not conducted to the auricle and the sinus retains control of that chamber.

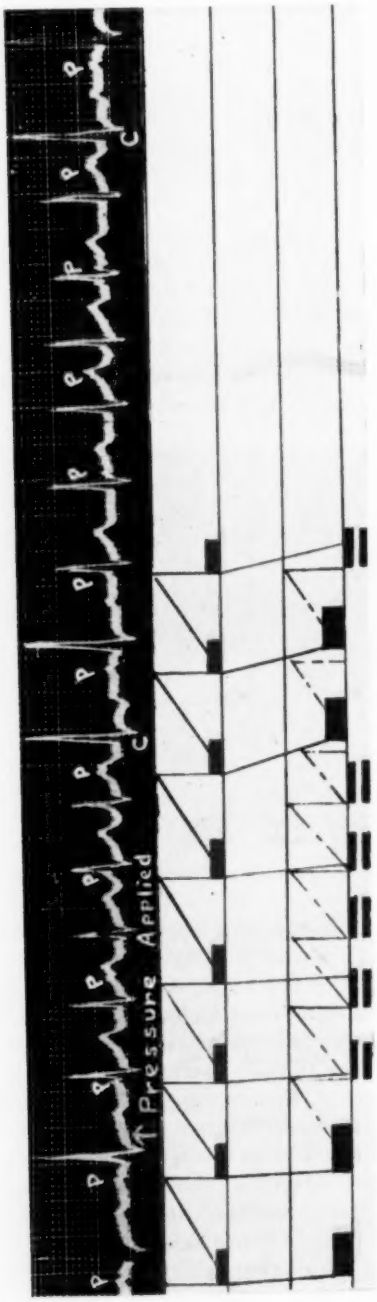

FIG. 8.—Independent rhythm with unidirectional block.

In these tracings, as in Fig 6, when an auricular impulse is so placed that it reaches the ventricle after its refractory phase and before the ectopic center has had time to develop an effective impulse the ventricle responds to the sinus node. This occurs wherever an auricular complex is superimposed on a *T* wave. The succeeding ventricular response is premature and a parasystole appears. This and the following ventricular complexes are the result of supraventricular stimulations. The third sinus impulse, however, is anticipated by a stimulus from the more rapid ectopic center and falls upon a refractory ventricle. The auricular rhythm continues

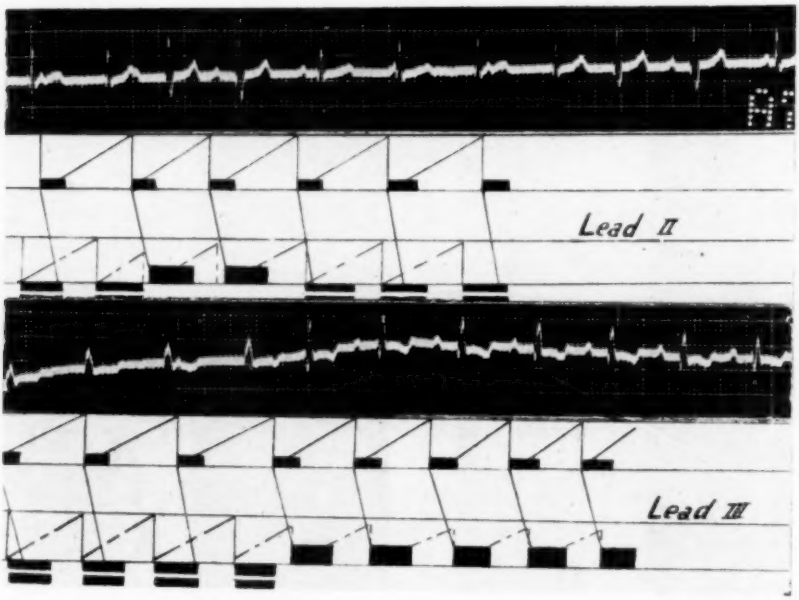

FIG. 9.—Transition from independent rhythm with unidirectional block to sinus rhythm.

undisturbed; the ventricular rhythm is periodically interrupted by premature beats (parasystoles). In Lead III of Fig. 8 the sinus regains control of the whole heart when its rate of stimulus production spontaneously increases to exceed the lower center. When the ectopic center dominates the ventricle the ventricular rate is 83 per minute, the auricular rate is 79. After the fourth ventricular complex the sinus node spontaneously accelerates to 86 per minute and regains control of the entire heart.

Figures 10 to 13 are illustrations in which the conducting tissue transmits impulses in either direction (Group II). Examples of that mechanism are rare but are not infrequently seen in cases where the dominating center is above the bifurcation of the bundle

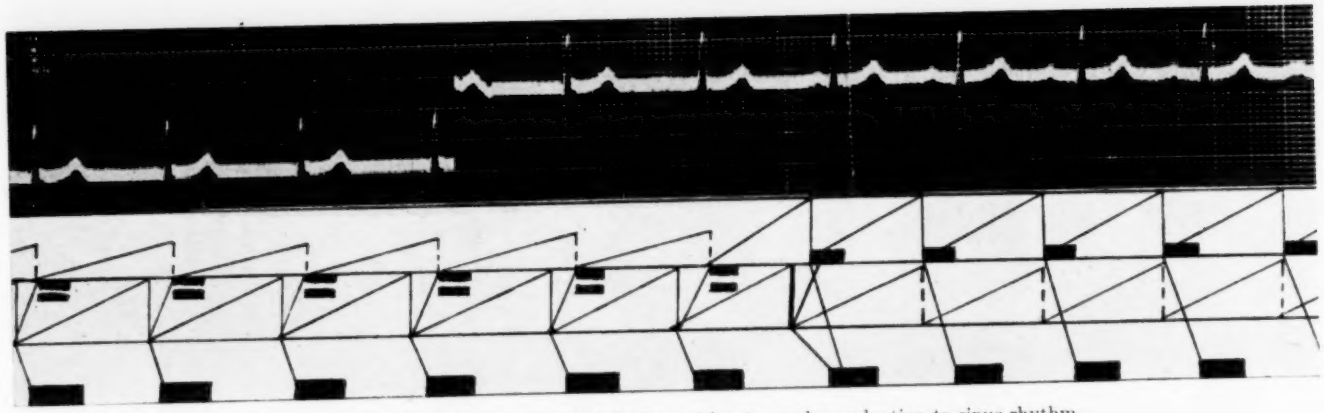

FIG. 10.—Transition from A–V nodal rhythm with retrograde conduction to sinus rhythm.

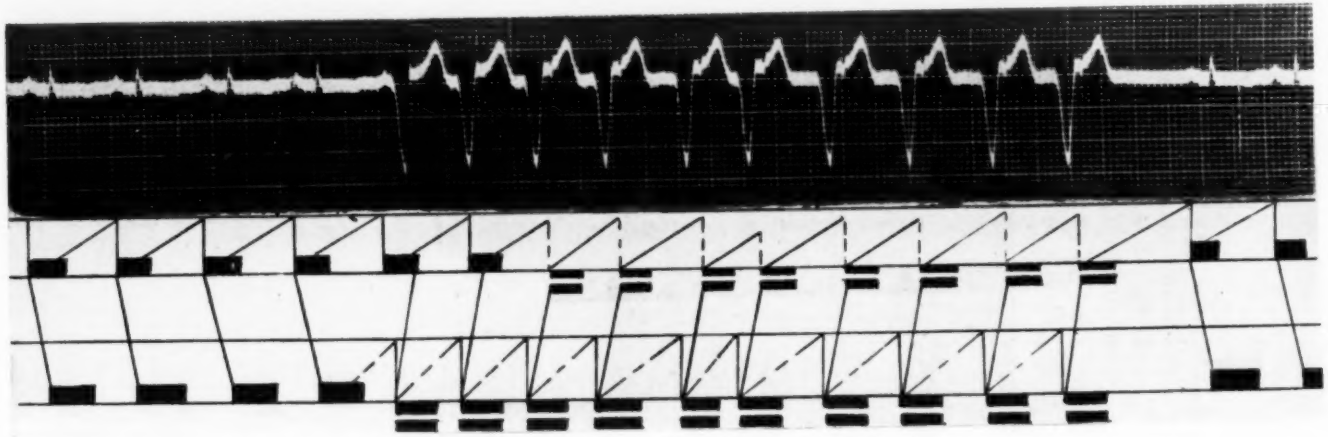

FIG. 11.—Ventricular tachycardia with retrograde conduction.

tissue. Such rhythms probably have their origin in the *A–V* node and the auricular response is in effect due to aberrant excitation from an abnormal auricular focus, rather than to a retrograde ventricular impulse. It is extremely rare to see examples in which the center of cardiac control is below the division of the bundle of His.

Figure 10 shows a paroxysm of low nodal rhythm (Group IIA 2*d*). The center dominates the entire heart, its impulses spreading downward to the ventricle and upward to the auricle. The sequence of contraction is reversed—the auricular complex appears upon and after the down stroke of the *R* wave. *A–V* nodal rhythm at a rate of 79 per minute continues through the 6th complex. At that point the sinus node accelerates its own rate to 86 per minute, regaining cardiac control. This, and the previous figure, illustrate that the most rapid center is dominant in the cardiac chamber in which it exists. It will control the entire heart if its impulses are conducted to the other chamber.

Figure 11 is an unusual example of complete cardiac control by a rapid ectopic ventricular center (Group IIB 4). Apparently retrograde conduction is unimpaired and equal to or closely equal to forward conduction. This is evidenced by the fact that the *P–R* and *R–P* intervals differ by 0.02 second. Impulses from the ventricle spread upward and replace the slower sinus node. The retrograde auricular response does not appear in the first two ectopic ventricular complexes because the retrograde impulse finds the auricle refractory.

Figure 12 is another very rare illustration of retrograde conduction and rhythm control by a lower ectopic center (Group in IIB 2). Here, however, ventricular control is affected by the depression of the sinoauricular node in a phasic arrhythmia, allowing for escape of a comparatively slow ectopic center. Occasionally the ventricle is stimulated simultaneously by an impulse from the auricle and by one from the ectopic center. When that occurs a "transition"[8] complex appears. Such is the interpretation given the last aberrant complex. When the rate of stimulus production in the sinus speeds up, as occurs at the end of the paroxysm, control of the rhythm reverts to the natural pacemaker. The interplay of these two centers continued over a long tracing in which one or the other gained control depending upon the rate at which the sinoauricular node builds up its impulses. Impulse formation in the ectopic center remained constant, cycle length 0.86 second, whereas the sinus cycle length varied between 0.75 and 0.96 second. The inverted deflections terminating aberrant *R* 2–6 are interpreted as retrograde auricular complexes. Where they fail to appear at the beginning and end of the paroxysm they do so because the auricle has responded to the sinus and is refractory to the retrograde impulses from the ventricle.

Fig. 11. Ventricular tachycardia with retrograde conduction.

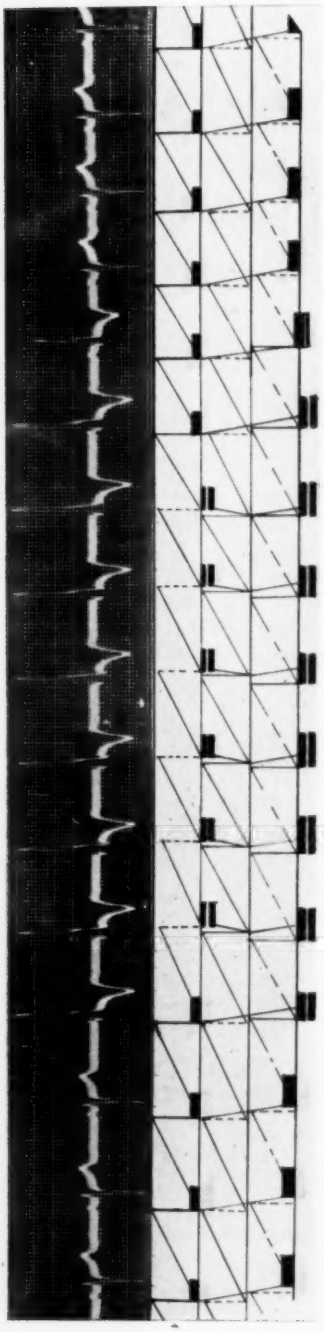

FIG. 12.—Escaped ventricular rhythm with retrograde conduction.

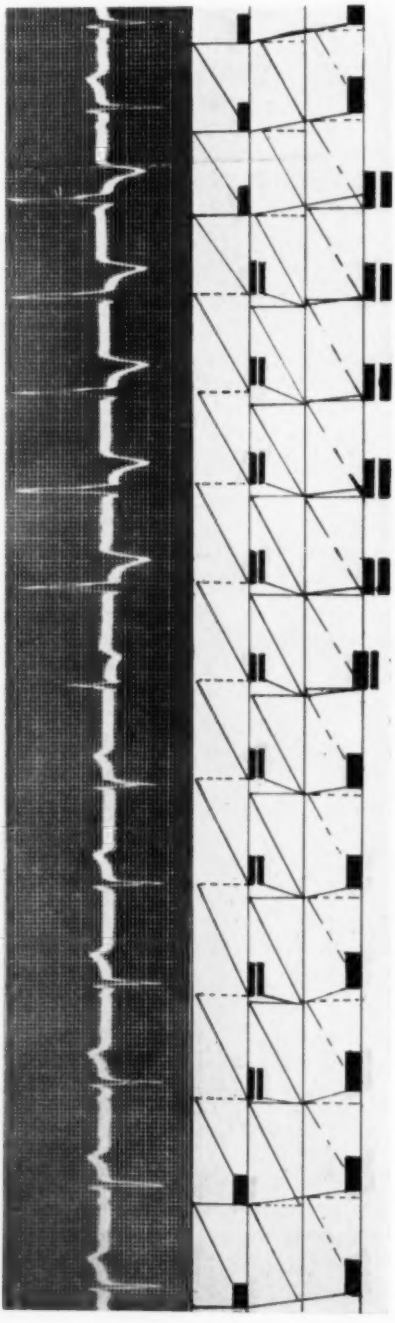

FIG. 13.—Escaped nodal and ventricular rhythm with retrograde conduction.

There is the possibility that these inverted complexes are retrograde from the node and not from the ventricle. If such is the mechanism the tracing illustrates independent rhythms in which the auricle is responding to the *A–V* node and the ventricle to an ectopic center. Figure 13 seems to support that interpretation. It is another paroxysm in the same patient. The first two ventricular complexes are of sinus origin; complexes 3 to 6 are of nodal and 7 is transitional. These are followed by a paroxysm of ectopic rhythm. The 3d and 4th auricular complexes are probably also transitional representing a response to impulses from the *S–A* and *A–V* nodes. It will be noted that the auricular complexes gradually shift from a position in front of the ventricular complex to one following and again to appear in its natural sequence when the sinus regains control. The absence of fixed relationship to the abnormal ventricular complex suggests that the auricle is beating independently. Another point which favors that interpretation is the fact that the *P–R* interval of the normal cycle exceeds the *R–P* interval of the ectopic cycle. One would have to assume the unlikely possibility that retrograde conduction is more rapid than forward. The fact that the auricular complexes are abnormal and at times inverted favors the *A–V* node as the pacemaker of the upper chamber. The manner in which the abnormal *P* waves shift into and then follow the *Q–R–S* complexes suggest the possibility that the site of impulse initiation in the node may be at several levels.[9]

In this tracing the depressor effect in a sinus arrhythmia is felt first by the sinoauricular node. When the latter is sufficiently slowed the *A–V* node escapes. Finally an ectopic ventricular center takes up the rhythm. It is not clear why the ventricular center did not submerge the *A–V* node from the start for the rate of the former is slightly higher. A possible explanation may be that the rapid auricular impulses not only submerges but depresses the ventricular center.[4] As the supraventricular impulses decrease in frequency the ventricular center accelerates its own rhythm until it escapes from supraventricular control.

In complete heart block (Group III) the chambers are independent and each has its own center of impulse formation. In the usual examples the sinus node controls the auricle and a center of slow rate situated above or below the bifurcation of the His bundle controls the ventricle. Ectopic centers may replace these and the usual relationship of auricular and ventricular rates may be reversed. Levine and Matton[10] published a remarkable case in which the ventricular rhythm either was or closely bordered upon ventricular fibrillation. In a case of complete heart block published by Kerr and Bender[11] both auricles and ventricles are fibrillating.

Figure 14 is an example of complete heart block in which the auricle is fibrillating and the ventricle is responding to its own rhythmic center, Group IIIA5 B2. Two reasons are offered for the

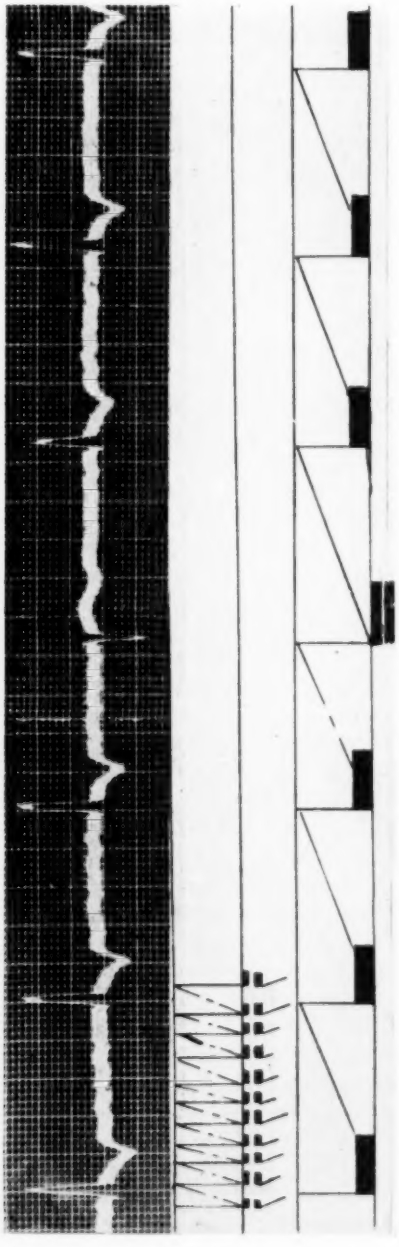

FIG. 14.—Complete heart block. Auricular rhythm—fibrillation.

interpretation here of complete heart block. First is the regularity of the ventricle cycle lengths which are 1.02 second. The second is the effect of a premature beat on this regularity. It will be observed that the interval succeeding the premature beat is exactly equal to the interval between two regular ventricular complexes. Such premature beats appeared frequently and in each instance the succeeding interval measured 1.02 second. This relationship is evidence against auricular control of the ventricle, for if the latter were the case, premature contractions of the ventricle could not interfere with the impulses from the fibrillating auricle except for the short period of refractoriness, and the succeeding intervals would vary dependent only upon the arrival of an effective auricular stimulus. Thus complete heart block best explains the mechanism in this tracing. The auricle is responding to a circus movement and the ventricle to an independent ventricular center which emits stimuli at regular intervals. When a premature extraneous impulse spreads through the ventricle it discharges the stimulus forming in the regular center and the latter must initiate a new impulse. The rate at which it develops impulses remaining constant it follows that the cycle length succeeding a premature contraction should be equal to that between two regular complexes.

Summary. Human electrocardiograms are described which illustrate the mechanism of the control of cardiac rhythm. They support the theory that the heart responds to the rhythm center which develops effective stimuli most rapidly. It is shown that a submerged slower center can gain control when its rate in relation to the others changes so that it becomes the most rapid. This is effected either by stimulation of the submerged center or depression of the dominating center.

The effect of the state of conduction on cardiac rhythm is shown and discussed.

Evidence for simultaneous activity of several centers is illustrated.

The following rare clinical examples of cardiac arrhythmia are shown:

1. Escape of an ectopic ventricular beat.
2. Escape of slow ventricular ectopic rhythm.
3. Transition from nodal rhythm to sinoauricular rhythm.
4. Transition from ectopic ventricular rhythm to sinus rhythm.
5. Transition from sinus rhythm to auricular flutter.
6. Retrograde conduction.
7. Unidirectional block.
8. Parasystole.
9. Complete heart block with auricular fibrillation.

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LEFT AXIS DEVIATION WITH AND WITHOUT HEART DISEASE.*

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In a study of the electrocardiogram in patients with obesity[1] it was observed that left axis deviation in the presence of an erect *T* wave in Lead III was generally found in patients with objective evidence of heart disease. When the *T* wave in Lead III was inverted the left axis deviation was found usually to be due simply to a change in the position of the heart. A further analysis of the significance of various associated features in the presence of left axis deviation indicated that in addition to the erect *T* wave in Lead III, a relatively low *T* wave in Lead I and a deep *S* wave in Lead II also were frequently found in the presence of heart disease.[2,3] In the present study, an attempt is made further to establish the clinical significance of these findings associated with left axis deviation.

One hundred and thirty-six electrocardiograms with left axis

* This study was made possible by a grant from the Bingham Associates Fund.

deviation were analyzed. In all cases the electrical angle calculated from the electrocardiogram, according to Einthoven, was less than 20 degrees.

Those patients were considered to have normal hearts in whom there was no clinical or roentgenologic evidence of heart disease and in whom the blood pressure was normal. The abnormal clinical cases were those in which there was either definite roentgenologic evidence of cardiac enlargement, a persistent elevation of the systolic blood pressure over 170 mm. Hg, or both. In the few questionable cases the systolic blood pressure was between 150 and 170 mm. Hg, with or without probable slight cardiac enlargement.

The attempt was chiefly to determine the significance of the presence or absence of the following: A low erect *T* wave in Lead I, the *T* wave being less than one-seventh of the amplitude of the *R* wave, an *S* wave in Lead II of at least one-half the amplitude of the *R* wave and an erect *T* wave in Lead III. Those cases were regarded as simple left axis deviation in which none of these findings were associated. Others were classified according to whether they showed one, two or all of the above signs. Aside from the left axis deviation and the findings above referred to, which in themselves are not indicative of heart disease, the electrocardiograms showed no abnormalities.

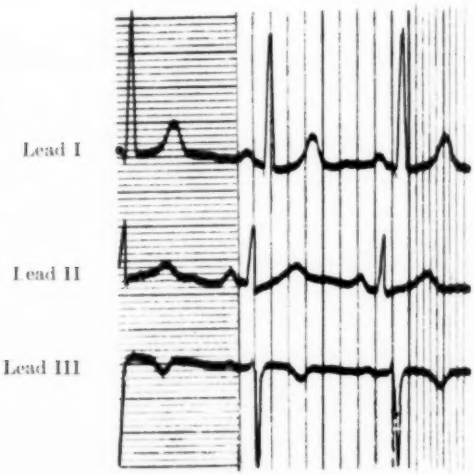

FIG. 1.—Left axis deviation of the type associated simply with change in the position of the heart. Note the relatively high *T* wave in Lead I, the absence of an *S* wave in Lead II and the inverted *T* wave in Lead III.

Results. *Left Axis Deviation With No Significant Changes* (Fig. 1). There were 24 cases of left axis deviation in which the *T* wave in Lead I was erect and prominent, the *T* wave in Lead III inverted

and the *S* wave in Lead II either absent or insignificant. In these 24 cases there was definite evidence of heart disease in only 2 and questionable evidence in 2.

In an evaluation of electrocardiograms from material such as we are analyzing, it is obvious that in a certain percentage of cases in which the electrocardiograms are entirely normal, there will be definite cardiac disease—first because most of the patients on whom electrocardiograms are obtained either have or are suspected of having heart disease and second because not infrequently even in the presence of advanced cardiac disease the electrocardiogram may be normal. The incidence of cases in which there was objective evidence of heart disease in the presence of a normal electrocardiogram was found to be 38% in 100 consecutive cases. In other words, slightly more than one-third of our normal electrocardiograms are found in patients with heart disease.

On the other hand, in only 17% (4 out of 24) of the cases of what we considered simple or insignificant left axis deviation was there evidence of heart disease. This unusually low incidence is due to the fact that a large number of these electrocardiograms were taken in cases of simple obesity. In the non-obese cases the incidence of cardiovascular abnormality in the presence of what is considered simple left axis deviation was 33%, which corresponds closely to the incidence of diseased hearts in the control series of normal electrocardiograms.

Left Axis Deviation With Significant Change in Only One Lead. There were 38 cases of left axis deviation in which only one of the signs above referred to was present, with definite evidence of cardiovascular disease in 27 (71%). In these 27 cases the significant change associated with the left axis deviation was a deep *S* wave in Lead II in 16 cases, an erect *T* wave in Lead III in 10 cases and a low *T* wave in Lead I in only 1 case. This 71% is contrasted with the 38% of normal electrocardiograms found in the presence of heart disease in the control group.

In the remaining 11 of the 38 cases in this group, 7 had no evidence and 4 only questionable evidence of heart disease. Of the 7 patients with no evidence of heart disease, 4 had a deep *S* wave in Lead II, and 3 in an erect *T* wave in Lead III; while of the 4 cases with questionable evidence of heart disease, 3 showed a deep *S* wave in Lead II and 1 an erect *T* wave in Lead III.

Left Axis Deviation With Significant Changes in Two Leads. There were 34 electrocardiograms showing left axis deviation in the presence of significant changes in at least two leads. In 27 (79%) of these cases there were objective signs of cardiovascular damage. In these cases no one grouping of associated electrocardiographic changes was considerably more frequent than another. In 9 of these cases the changes were in the *T* waves in Leads I and III; in 10 cases the changes were in the *S* wave in Lead II and the *T*

wave in Lead III, and in 8 cases the changes were in the *T* wave in Lead I and the *S* wave in Lead II. Of the 7 cases in this group in which the blood pressure and heart were normal the electrocardiographic changes were found in the *S* wave in Lead II and the *T* wave in Lead III in 6, and in the *T* wave in Lead I and *S* wave in Lead II in the remaining case.

Left Axis Deviation With Significant Changes in All Leads (Fig. 2). There were 40 cases of left axis deviation in which changes were observed in all leads. In 38 (95%) there was obvious cardiovascular disease. This incidence of disease is sufficiently striking to warrant considering such electrocardiograms regularly as distinctly abnormal.

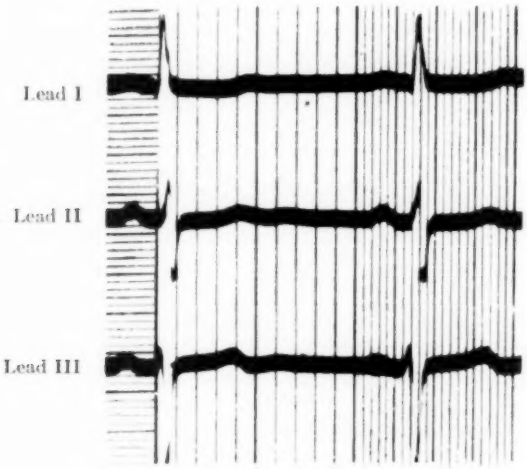

FIG. 2.—Left axis deviation of the type generally associated with myocardial disease. Note the relatively low *T* wave in Lead I, the prominent *S* wave in Lead II and the erect *T* wave in Lead III.

Results of Follow-up Studies. In 28 cases we were able to obtain two or more electrocardiographic records over periods varying from 7 months to 4 years. Of these 28 cases, 22 had evidence of heart disease; 13 of the 22 showed progressive changes of one type or another. There was nothing in their clinical course to indicate that the progressive changes in the electrocardiograms might have been due to coronary occlusion nor could the changes be attributed to digitalis effect. In 6 of the 22 cases initial changes were present in all three leads. In all of these cases the *T* wave in Lead I became lower (to the point of inversion in 1 case), while in 5 of the cases the *T* wave in Lead III became more positive and in 1 the *S* wave in Lead II became deeper. In a study of progressive myocardial disease, Willius[4] illustrates the development of an inverted *T* wave in Lead I in 9 months in a patient whose initial electrocardiogram,

considered "essentially normal," showed left axis deviation with the changes in the three leads above described.

In 7 cases in which there were initially a low T wave in Lead I and an erect T wave in Lead III, the T wave in Lead III became

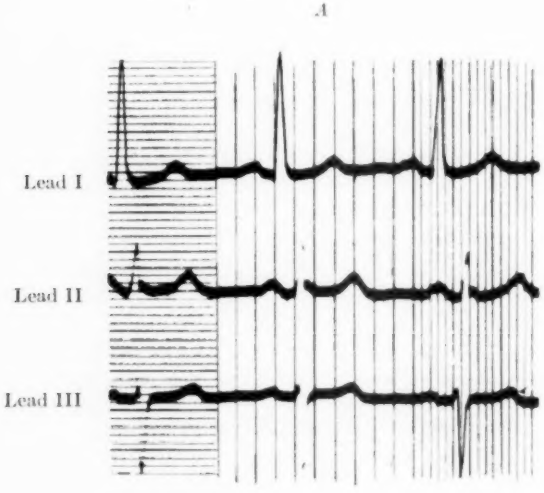

FIG. 3 *A*.—Left axis deviation with a relatively low T wave in Lead I and an erect T wave in Lead III in the presence of hypertensive heart disease with moderate cardiac enlargement.

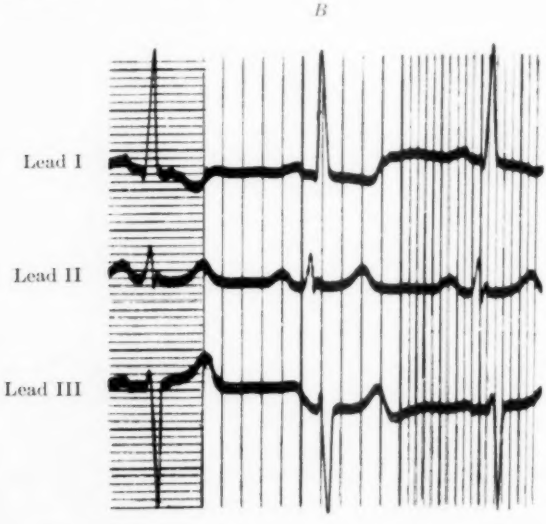

FIG. 3 *B*.—An electrocardiogram taken 19 months later on the same patient, showing the development of an inverted T wave in Lead I, a slight S wave in Lead II and a more prominently erect T wave in Lead III.

more positive in 4 cases while the *T* wave in Lead I became lower, in 1 case actually becoming negative (Fig. 3). In the remaining 3 of these 7 the *S* wave in Lead II became deeper. Nine of the 22 cases which had evidence of heart disease showed no change on successive electrocardiograms. Of these 9, 2 had initially what we termed "simple left axis deviation;" 1 had only a deep *S* wave in Lead II, 2 showed changes in the *T* wave in Lead I and the *T* wave in Lead III, and 4 showed changes in all leads.

In 6 of the total 28 cases in which repeated electrocardiograms were observed there was no evidence of heart disease nor were there any significant changes associated with the left axis deviation. In these cases, over a period of 3 to 4 years, no progressive changes were observed in the electrocardiograms.

Discussion. In 1921, Herrmann and Wilson[5] observed that while rotation of the heart produced in the *P* and *T* waves changes similar to those which it produced in the *Q–R–S* waves, ventricular preponderance did not affect *P* waves and its effect upon *T* waves was uncertain. Cohn and Raisbeck[6] concluded similarly, in regard to the *Q–R–S* and *T* wave relationship, that the form and direction of the *T* wave in preponderance curves of enlarged hearts did not change in so simple a manner on rotating leads on the chest wall (thus simulating the change in position of the heart in the chest wall) as was the case in a normal subject. They thought this was perhaps because the *T* waves in the first place were not so prominently and in the second place not so simply formed. Bland and White[7] noted that a total inversion of Lead III was usually associated simply with change in the position of the heart. While this is true of total inversion, it appears likewise to be true of inversion only of the *Q–R–S* and *T* waves.[1]

There is, therefore, adequate evidence to indicate that when the *Q–R–S* and *T* waves behave uniformly as the electrical axis changes, the change in axis is due simply to change in the position of the heart. This appears to be true not only of the *Q–R–S–T* wave relationship in Lead III but in Lead I as well.[2]

In the presence of myocardial disease, however, there is a disturbance in the *Q–R–S–T* relationship manifested chiefly by a tendency for the *T* wave to assume a direction opposite to that of the initial ventricular complex.[2,8] Probably this is in some way associated with a disturbance in conduction of the ventricular muscle, a disturbance in the pathway of retreat. (The tendency of the initial and final ventricular phases to assume opposite directions in the presence of conduction disturbance in one of the bundle branches is associated with a spreading of the initial complex and is probably not directly related to the mechanism here referred to.) We should anticipate, therefore, in the presence of left axis deviation with myocardial disease that the *T* wave in Lead I would either fail to increase in amplitude or would actually decrease as the *R* wave

in Lead I becomes more positive, also that the *T* wave in Lead III would fail to become negative or actually would become more positive as the *Q–R–S* wave in Lead III becomes more negative. Such a disturbance in the behavior of the two phases of the ventricular complex in the presence of left axis deviation would seem to have the same significance as the development of an inverted *T* wave in Lead I, for example, which likewise represents simply a disturbance in the normal *Q–R–S–T* relationship and is generally thought to be due to myocardial damage, though Barnes and Whitten[9] might account for such a change as well as the progressive changes above described as due probably to a progressive hypertrophy of the left ventricle. It is, however, reasonable to assume that where there is a relatively low *T* wave in Lead I and an erect *T* wave in Lead III in the presence of left axis deviation of the *Q–R–S* wave there is evidence of myocardial change, either hypertrophy or some other form of disease.

Just what the significance of the prominent *S* wave in Lead II is in this connection we are not prepared to say. It appears to be in some way associated with cardiac abnormalities in the same manner as the *T*-wave disturbances above referred to. Wilson, Macleod, Barker, Johnston and Klostermeyer,[10] later Winternitz,[11] reported changes in the initial deflection of the ventricular complex in myocardial infarction. Perhaps the change in *S* wave in Lead II here described bears the same relation to such changes as Wilson and his coworkers reported (more particularly the "Q_1" type) as the slowly developing, roundly inverted *T* wave bears to the characteristic rapidly developing sharply inverted *T* waves in the presence of acute infarction. In 1 case the myocardial changes develop relatively rapidly, in the other slowly. In both cases, however, the electrocardiographic changes signify myocardial disease.

Summary. 1. Electrocardiograms showing left axis deviation with no other abnormal findings were analyzed with particular reference to the presence or absence of a relatively low erect *T* wave in Lead I, a prominent *S* wave in Lead II and an erect *T* wave in Lead III.

2. The analysis indicates that in the absence of any of the three changes above enumerated the left axis deviation is not associated with cardiovascular disease. In the presence of one of the changes the incidence of associated cardiovascular disease is considerable, in the presence of two changes it is greater, while the presence of all three changes constitutes almost invariable evidence of heart disease.

3. Observations of repeated electrocardiograms taken over periods varying from 7 months to 4 years show the development of these associated changes in the presence of progressive cardiovascular disease.

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ELECTROCARDIOGRAPHIC CHANGES FOLLOWING THE ADMINISTRATION OF POTASSIUM IODID IN SYPHILITIC HEART DISEASE.

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This case is presented as evidence of marked change taking place in the syphilitic heart, following the administration of potassium iodid, even in comparatively small doses.

Case Report. The patient, a man aged 55, when first seen on February 1, 1934, complained of shortness of breath. This condition was noticed some 3 months before, when climbing stairs. At that time he was given "green drops" by his physician and felt better within a week. He returned to work and had no further trouble until the week preceding the present visit, when he began to experience shortness of breath at night. He dreamed, and wakened with a feeling of smothering. After sitting up for an hour or more, he could go back to sleep. He experienced no difficulty when walking on the level, but climbing two flights of stairs caused trouble.

The patient's *family history* revealed nothing of note. His *past history* was negative, except for a gonorrheal infection contracted when he was a boy. He had successfully passed a life insurance examination 31 years ago. His wife was living and in good health and had had no miscarriages; he had four children living, all of whom are healthy.

Physical examination revealed a small, thin man, in no apparent distress. His right pupil was slightly larger than the left. Reaction to light was sluggish. There were no palpable glands. His teeth were in bad condition. A rather marked pulsation in the vessels of the neck was noted. The apex beat was felt in the fifth and sixth intercostal space, well outside the midclavicular line. No thrills and no shocks were present. The heart rate, when standing, was 96, the rhythm regular. A short, systolic murmur could be heard at the base on each side of the sternum, followed by a blowing, diastolic murmur, loudest over the aortic area and transferred downward on each side; this murmur was especially noticeable in the fourth intercostal space, to the left, near the sternum. When the patient was lying down, a faint systolic murmur at the apex could also be heard. His pulse was of the Corrigan type. The arteries were thickened. The blood pressure in the left arm was 150/50 and in the right arm 140/60. Examination of the lungs revealed coarse râles over both sides of the chest; a few moist râles could be noted at the bases, posteriorly. Knee jerks were present. The abdomen showed nothing abnormal and there was no edema of the extremities. The Wassermann reaction was positive (++++). A faint trace of albumin was found in the urine. Fluoroscopic examination of the chest revealed enlargement of the left ventricle and some dilatation of the aorta.

The electrocardiogram made on the day the patient was first seen is shown in Fig. 1. The following day he began taking bichlorid of mercury, $\frac{1}{24}$ grain and potassium iodid, 10 grains, 3 times daily.

The patient returned after 16 days of comparative inactivity feeling somewhat better. The electrocardiogram made at this time (Fig. 2) showed inversion of the *T* wave in Leads I and II and almost flat *T*-3. Medication with potassium iodid and mercury was discontinued on February 17.

On March 3, the patient reported having experienced one attack of dyspnea at night. Physical examination showed no change. In the electrocardiogram (Fig. 3) the *T* waves were upright in Leads II and III and diphasic in Lead I. Administration of bichlorid of mercury and potassium iodid was resumed in the same dosage.

The patient, when seen on March 10 was feeling about the same. In the electrocardiogram taken on this day (Fig. 4), the changes in the *T* waves in all leads can be noted. Dosage of potassium iodid was increased to 15 grains 3 times daily, continuing the bichlorid of mercury as before.

On March 17, the patient reported feeling much improved. The electrocardiogram of this date (Fig. 5) shows an increase in the inversion of the *T* wave in Leads I and II, approaching that of the coronary type. Administration of mercury and potassium iodid was discontinued.

On March 24, some dyspnea was reported. Fig. 6 of this date shows the *T* wave upright in Leads II and III and diphasic in Lead I. The same dosage of bichlorid of mercury was resumed with 15 grains of potassium iodid 3 times a day.

The patient reported feeling much better on March 31. The physical examination showed no variance. Marked changes in the *T* waves in all leads are to be noted in Fig. 7. Medication was discontinued.

On April 7, he felt not quite so well, although the physical examination showed no change. The differences in the *T* waves at this time are shown in the electrocardiogram in Fig. 8. Potassium iodid (15 grains, 3 times daily) without mercury was prescribed.

On April 14, the patient reported one attack of dyspnea without definite change in the findings of physical examination. The variations in the *T* wave in all leads when he was taking potassium iodid without mercury are to be noted in Fig. 9. Potassium iodid was discontinued and administration of $\frac{1}{24}$ grain of bichlorid of mercury, 3 times daily, was resumed.

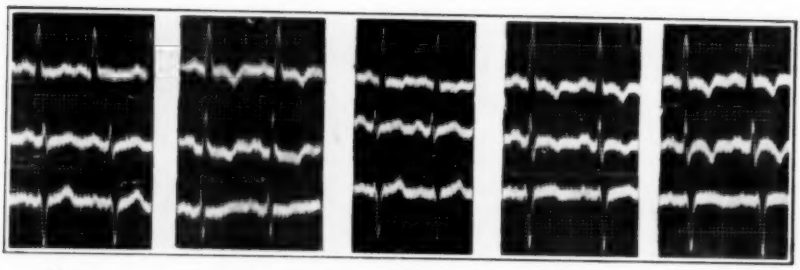

Fig. 1.
2–1–34.

Fig. 2.
2–17–34.

Fig. 3.
3–3–34.

Fig. 4.
3–10–34.

Fig. 5.
3–17–34.

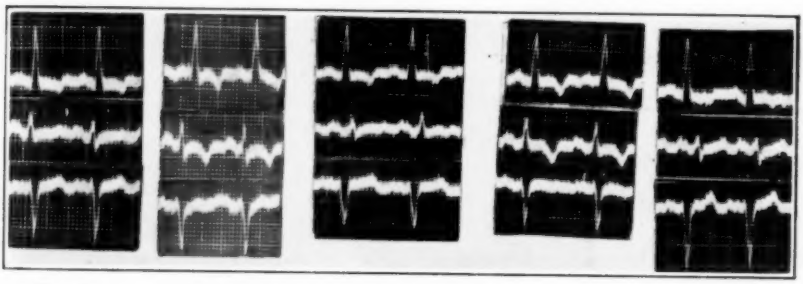

Fig. 6.
3–24–34.

Fig. 7.
3–31–34.

Fig. 8.
4–7–34.

Fig. 9.
4–14–34.

Fig. 10.
4–21–34.

The patient reported increased shortness of breath on April 21. From the electrocardiogram (Fig. 10), it can be seen that the *T* waves had become upright in Leads II and III and were only slightly inverted in Lead I.

It would therefore seem that the potassium iodid was the cause of the variations in the *T* waves, since they occurred when he was taking potassium iodid without mercury and disappeared when he took mercury without potassium iodid. During the course of this study the patient remained at home in comparative inactivity. It is believed that the changes seen in these curves are brought about by the effect of the potassium iodid on the luetic lesion near the orifices of the coronary arteries. When the use of potassium iodid was discontinued the reaction subsided, the blood supply to the ventricles was reëstablished and the marked changes in the *T* waves disappeared. Other minor changes in the form of the curves may be noted, but the *T* waves were the chief interest in this study.

The patient has not returned for further observation.

Summary. A case of luetic heart disease is presented, showing marked changes in the electrocardiogram, following the administration of potassium iodid, which disappeared when the potassium iodid was stopped, to recur when the iodid was renewed. It is believed that further study will cause a change in the prevalent ideas regarding the treatment of this condition, and that such a study may also be useful in diagnosis. No similar changes in other heart conditions have been noted, in the few cases observed.

AURICULAR FIBRILLATION IN HYPERTHYROIDISM.

THE INFLUENCE OF AGE.

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AND

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HYPERTHYROIDISM has long been recognized as one of the common causes of auricular fibrillation. In a recent study by one of us (Smith) hyperthyroidism ranked second as a cause of this cardiac arrhythmia. The exact incidence of auricular fibrillation in hyperthyroidism has varied considerably in different localities and in the clinical material studied by different investigators. The present study was undertaken to determine the influence of age in the production of auricular fibrillation among patients with hyperthyroidism. The clinical material providing the basis for the study consisted of cases in which operation was performed, of exophthalmic goiter and of hyperfunctioning adenomatous goiter. The aim was to take for study 100 cases of exophthalmic goiter, representing each of the first eight decades of life, or 800 cases in all, and a similar number, similarly distributed, of cases of hyperfunctioning

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adenomatous goiter. However, in some decades of life 100 cases were not available. Adenomatous tissue in the thyroid gland rarely produces hyperthyroidism before the age of 20; few patients with such a condition were in the second decade of life and none in the first. Although exophthalmic goiter is not so uncommon before the age 20, only a few patients were in the first decade of life. For various other reasons, the number of patients with exophthalmic goiter and the number with hyperfunctioning adenomatous goiter who were in the eighth decade of life fell short of 100.

Classification. The presence of auricular fibrillation in hyperthyroidism by no means precludes a return to normal sinus rhythm. In many cases a transient period of auricular fibrillation occurs during the immediate postoperative interval, and at no other time. Cases of this type comprise the larger part of the group we have classified as instances of intermittent auricular fibrillation. We have also included in this group those patients who had auricular fibrillation before as well as after operation, and whose cardiac rhythm returned to normal following thyroidectomy. The preoperative period of fibrillation of some of these patients was of fairly long standing; of others, it was limited to one or more paroxysmal attacks. Undoubtedly many patients with hyperthyroidism have short periods of auricular fibrillation which the clinician has no opportunity to observe.

Those patients with auricular fibrillation, whose arrhythmia was constantly present during the time the patient was under observation, we have classified as having continuous auricular fibrillation. The period of observation usually comprised several days to 3 weeks before operation, and 2 to 3 weeks after operation. Later observations make it certain that in some cases of prolonged auricular fibrillation, normal sinus rhythm is reëstablished after a greater length of time. In other cases the auricles fibrillate indefinitely. The number of patients whose normal cardiac rhythm is reëstablished after leaving the clinic cannot be accurately determined.

Age. Table 1 shows the incidence by decades of auricular fibrillation in exophthalmic goiter and in hyperfunctioning adenomatous goiter. It also shows the relative incidence, by decades, of the continuous and intermittent types of auricular fibrillation found in each type of hyperthyroidism, as well as the number of postoperative deaths of patients with auricular fibrillation.

Auricular fibrillation was absent before the age of 20, uncommon before the age of 40 and very frequent after the age of 50. Rising rapidly in the sixth decade, the incidence of auricular fibrillation continued to mount during the seventh decade and reached a maximum of about 50% in the eighth decade.

Table 2 shows the incidence by decades of auricular fibrillation in exophthalmic goiter and in hyperfunctioning adenomatous goiter after exclusion of certain complicating factors.

TABLE 1.—AGE INCIDENCE OF AURICULAR FIBRILLATION IN HYPERTHYROIDISM.

Decade of life.	Exophthalmic goiter.						Hyperfunctioning adenomatous goiter.					
		Auricular fibrillation.						Auricular fibrillation.				
	Cases.	Cases.	Per cent.	Postoperative deaths.	Continuous fibrillation.	Intermittent fibrillation.	Cases.	Cases.	Per cent.	Postoperative deaths.	Continuous fibrillation.	Intermittent fibrillation.
0–9	13	0	0	0	0	0	0	0	0	0	0	0
10–19	100	0	0	0	0	0	15	0	0	0	0	0
20–29	100	3	3	0	0	3	100	2	2	0	0	2
30–39	100	1	1	0	0	1	100	5	5	0	0	5
40–49	100	4	4	0	3	1	100	11	11	0	2	9
50–59	100	22	22	1	11	11	100	33	33	2	8	25
60–69	100	29	29	1	9	20	100	50	50	0	23	27
70–79	22	12	55	2	5	7	82	38	48	4	14	24

TABLE 2.—AGE INCIDENCE OF AURICULAR FIBRILLATION IN HYPERTHYROIDISM AFTER EXCLUSION OF POSSIBLE ASSOCIATED ETIOLOGIC FACTORS OF HYPERTENSION, ARTERIOSCLEROSIS, ENDOCARDITIS AND PERICARDITIS.

Decade of life.	Exophthalmic goiter.			Hyperfunctioning adenomatous goiter.		
	Auricular fibrillation.		Total.	Auricular fibrillation.		Total.
	Continuous.	Intermittent.		Continuous.	Intermittent.	
0–9	0	0	0	0	0	0
10–19	0	0	0	0	0	0
20–29	0	2	2	0	2	2
30–39	0	1	1	0	4	4
40–49	0	1	1	1	7	8
50–59	8	9	17	3	17	20
60–69	5	13	18	7	17	24
70–79	4 (18%)	5 (23%)	9 (41%)	7 (8%)	12 (15%)	19 (23%)

Incidence of Auricular Fibrillation in Exophthalmic Goiter and in Hyperfunctioning Adenomatous Goiter. Whether hyperthyroidism is on a basis of adenomatous or of exophthalmic goiter, the patient who is over 50 is likely to have auricular fibrillation. The influence of age on the incidence of auricular fibrillation is similar in the two types of hyperthyroidism, considered separately.

Auricular fibrillation occurred more frequently in association with hyperfunctioning adenomatous goiter than in association with exophthalmic goiter in almost every decade of life. The slightly higher incidence of 3% in association with exophthalmic goiter in the third decade, as compared with 2% in association with hyper-

functioning adenomatous goiter in the same age group, is too small to be considered significant. The apparently higher incidence of 55% in cases of exophthalmic goiter in the eighth decade, as compared with 48% in cases of hyperfunctioning adenomatous goiter, may be due to the small group of cases of exophthalmic goiter (22) which was available for study, as compared with the larger group of cases of hyperfunctioning adenomatous goiter (82).

Incidence of Continuous and Intermittent Types of Auricular Fibrillation. The cases in which auricular fibrillation was intermittent outnumbered those in which it was continuous, both among those of exophthalmic and among those of hyperfunctioning adenomatous goiter, and in younger as well as older age groups.

Advancing age determines an increase in frequency of occurrence of cases of intermittent and also of continuous auricular fibrillation.

No patient under 40 was found to have continuous auricular fibrillation. Among the handful of patients in the third and fourth decades of life arrhythmia was a temporary departure from the normal.

TABLE 3.—DURATION OF INTERMITTENT AURICULAR FIBRILLATION OCCURRING FOLLOWING THYROIDECTOMY.

Decade of life.	Exophthalmic goiter.				Hyperfunctioning adenomatous goiter.			
	Cases.	Duration of auricular fibrillation, days.			Cases.	Duration of auricular fibrillation, days.		
		Minimum.	Maximum.	Average.		Minimum.	Maximum.	Average.
0–9	0	0	0	0	0	0	0	0
10–19	0	0	0	0	0	0	0	0
20–29	3	1	3	2.0	2	1.0	4	2.5
30–39	1	4	4	4.0	5	1.5	4	3.1
40–49	1	3	3	3.0	9	1.0	8	3.4
50–59	11	1	8	3.5	25	1.0	41	4.6
60–69	20	1	6	2.2	27	1.0	14	3.8
70–79	7	1	11	4.0	24	1.0	25	4.1

Duration of Auricular Fibrillation Following Thyroidectomy. In many cases in which transient fibrillation of the auricles developed following thyroidectomy, the abnormal rhythm lasted only a few hours. In a few it persisted as long as 10 days. Accurate observations regarding the duration of the period of fibrillation had not been noted in the records of all cases. Table 3 shows the average duration of postoperative auricular fibrillation for the patients in each decade. The hearts of patients with hyperfunctioning adenomatous goiter usually required longer to reëstablish a normal rhythm than did those of patients with exophthalmic goiter; this tendency was noticeable not only for the series as a whole, but in almost every decade.

Cardiac Decompensation. Cardiac decompensation of varying severity occurred in 25 of the 71 cases of exophthalmic goiter with auricular fibrillation; and in 37 of the 139 cases of hyperfunctioning adenomatous goiter with auricular fibrillation. Cardiac decompensation probably resulted in 33 of these 62 cases from a combination of hyperthyroidism and complicating disease of the heart. In 15 cases of exophthalmic goiter and in 14 of hyperfunctioning adenomatous goiter no cause for the cardiac decompensation other than hyperthyroidism could be found.

Influence of Hypertension and Intrinsic Cardiac Disease. Of 85 patients who had hyperthyroidism associated with hypertension, arteriosclerosis, endocarditis or pericarditis, 77 (91%) were over 50. Of 125 patients who had hyperthyroidism associated with none of these extraneous factors, 107 (86%) were over 50. In the case in which circulatory reserve has been reduced by previous organic heart disease, it is not surprising that the added burden of hyperthyroidism should result in myocardial insufficiency. That the increased incidence of auricular fibrillation, cardiac enlargement and decompensation among patients with hyperthyroidism who are over 50 is to be attributed wholly to the frequent occurrence of hypertension and coronary sclerosis at this period of life would appear to be incorrect. A large number of older patients with hyperthyroidism who had auricular fibrillation or other manifestations of cardiac injury gave no evidence of hypertension or of previous independent heart disease.

Influence of Duration and Intensity of Hyperthyroidism. Plummer has pointed out that although the onset of exophthalmic goiter is, as a rule, relatively acute, the onset of hyperthyroidism in adenomatous goiter is usually insidious; that in the former condition, patients come under observation on an average of 9 months after the onset of the goiter, whereas in the latter they come under observation on an average of 17 years after the appearance of the goiter, and on an average of 3 years after the onset of toxic symptoms. He wrote: "The latter complex (hyperfunctioning adenomatous goiter) may extend over months without attracting much attention; on the other hand, exophthalmic goiter brings the patient to the physician relatively early and with a syndrome readily interpreted."

Auricular fibrillation and cardiac decompensation resulting from hyperfunctioning adenomatous goiter may not be associated with any definite symptoms of hyperthyroidism. In such cases a considerable length of time often elapses before it is recognized that the goiter is the cause of the myocardial injury. The higher incidence of auricular fibrillation and of other signs of myocardial insufficiency in hyperfunctioning adenomatous goiter, as compared with exophthalmic goiter, is due chiefly to the different distribution by age in the two diseases (Table 4); 78% of patients with hyperfunctioning adenomatous goiter are over 40, whereas 61% of patients

with exophthalmic goiter are under 40. However, if patients in similar age groups are compared, there is a slightly higher incidence of auricular fibrillation in association with hyperfunctioning adenomatous goiter than in association with exophthalmic goiter. One cause for this may be the longer duration of hyperthyroidism in adenomatous goiter. Some writers are inclined to ascribe major importance to duration of hyperthyroidism as a factor in the production of myocardial injury. Anderson, in a recent study, concluded that the presence of auricular fibrillation among patients with hyperthyroidism seems to depend on two factors: (1) Duration of symptoms, and (2) severity of the condition. Andrus found that the average duration of symptoms was conspicuously greater among patients with myocardial insufficiency. Without a control series, analysis of the 210 cases of auricular fibrillation in our series does not permit definite conclusion in regard to the influence of duration and intensity of hyperthyroidism in the production of myocardial injury. However, our data indicate that age is a much more important factor than duration of symptoms or than intensity of hyperthyroidism.

TABLE 4.—INFLUENCE OF INTENSITY AND DURATION OF HYPERTHYROIDISM ON INCIDENCE OF AURICULAR FIBRILLATION.

Decade of life.	Exophthalmic goiter (cases with auricular fibrillation).			Hyperfunctioning adenomatous goiter (cases with auricular fibrillation).		
	Average basal metabolic rate.	Average duration of hyperthyroidism, mos.	Percentage of cases of exophthalmic goiter in which auricular fibrillation occurred.	Average basal metabolic rate.	Average duration of hyperthyroidism, mos.	Percentage of cases of hyperfunctioning adenomatous goiter in which auricular fibrillation occurred.
0–9	...	...	0	...	...	0
10–19	...	...	0	...	...	0
20–29	+46	14	3	+51	14	2
30–39	+28	9	2	+25	26	4
40–49	+30	3	3	+41	21	11
50–59	+38	25	21	+30	28	33
60–69	+39	15	30	+31	31	50
70–79	+44	15	54	+34	38	48
Averages for entire group with auricular fibrillation	+39	14	...	+32	31	

The average duration of symptoms and the average basal metabolic rates for the patients who had auricular fibrillation, cardiac enlargement and cardiac decompensation are given in Table 5.

TABLE 5.—DURATION OF SYMPTOMS AND METABOLIC RATES OF PATIENTS WITH VARIOUS CARDIAC CONDITIONS.

	Exophthalmic goiter.		Hyperfunctioning adenomatous goiter.	
	Duration of symptoms, mos.	Metabolic rates, %	Duration of symptoms, mos.	Metabolic rates, %
Intermittent auricular fibrillation	14 3	+39 5	31 1	+32 8
Continuous auricular fibrillation	16 6	+40 0	32 0	+33 5
Cardiac enlargement	15 8	+40 2	22 4	+33 8
Cardiac decompensation	19 3	+41 5	24 6	+38 6

The fact that for comparable age groups there is a higher incidence of auricular fibrillation in association with hyperfunctioning adenomatous goiter than in association with exophthalmic goiter indicates, when considered in conjunction with the lower basal metabolic rates which obtain in adenomatous goiter, that intensity of hyperthyroidism is not a very important factor in producing the arrhythmia. The duration of the period of auricular fibrillation and the chance of the arrhythmia being replaced by normal sinus rhythm are probably not greatly influenced by the basal metabolic rate.

Conclusions. Subjected to the effects of hyperthyroidism, old patients are prone to have auricular fibrillation; young patients, to maintain normal cardiac rhythm. The increased incidence of auricular fibrillation among older patients with hyperthyroidism is only partially attributable to the frequent occurrence of coronary sclerosis and hypertension after the age of 40. Advanced age itself, although unaccompanied by these processes, determines an increased susceptibility of the heart to auricular fibrillation and adds to the likelihood of its becoming decompensated under the stress of hyperthyroidism.

Among 210 cases of auricular fibrillation associated with hyperthyroidism, cardiac enlargement occurred in 79, in 35 of which there was no evidence of hypertension or of preëxisting cardiac disease. In the same group of cases of auricular fibrillation, cardiac decompensation was present in 62; in 29 of these, hyperthyroidism was the only cause found for the cardiac decompensation. In only 2 cases did cardiac enlargement or decompensation afflict patients under 40.

Auricular fibrillation resulting from hyperthyroidism is more often transient or intermittent than prolonged or continuous, especially when not accompanied by serious myocardial injury. The arrhythmia often develops, for the first time, during the immediate postoperative period, in which case it ceases spontaneously within a few hours to a few days. Even when cardiac injury has occurred, the fibrillation of the auricles is frequently

replaced by normal sinus rhythm, when the heart has been relieved of the strain of hyperthyroidism.

Hyperfunctioning adenomatous goiter results in auricular fibrillation and other signs of myocardial insufficiency more often than does exophthalmic goiter. This different incidence in the two types of goiter results mainly because patients with adenomatous goiter acquire hyperthyroidism on an average of about a decade later in life than do those with exophthalmic goiter. The longer duration of hyperthyroidism in adenomatous goiter is a less important factor in producing the higher incidence of myocardial injury in this disease. Advanced age seems a much more important factor than duration or intensity of symptoms in determining the incidence of auricular fibrillation and myocardial insufficiency of patients with hyperthyroidism.

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OBSERVATIONS ON PROGNOSIS IN ANGINA PECTORIS.

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Studies dealing with prognosis in angina pectoris are not lacking. The present report, which will be presented without reference to existing literature, is deemed of interest because it comes from a cardiac clinic in which arteriosclerotic heart disease is the predominant type. The average age of patients for whom a diagnosis of organic cardiovascular disease is made is 58 years. Approximately one-sixth of these patients include among their symptoms pain, either effort pain or pain related to coronary thrombosis. This study is based on the records of 166 patients who complained of effort angina. The term angina pectoris is used as Heberden described it and care has been taken to exclude those in whom effort pain first appeared after coronary thrombosis. It is hardly

necessary to state that there are undoubtedly errors in diagnosis and in the given causes of death. It is also recognized that the series itself is too small for mathematical treatment. Because of this fact and the unavoidable errors inherent in any such clinical study it is emphasized that the various figures given can have at best qualitative and never quantitative values.

Of these 166 patients, only 23 (about 14%) were women. The relatively low incidence of true angina in women is well known, but this small figure is the more striking because women constitute about 56% of the patients of this institution, and men, 44%. Of those suffering from cardiovascular disease, however, men predominate and the figures just given are reversed. The clientele of the institution does not represent a true cross-section of society, and any classification of this group on the basis of occupation would not be of significance for the social distribution of the disorder under consideration, but such classification does, however, confirm certain current impressions. The largest single group, 71 cases, comprised business men and executives. The second largest group was that of the physicians, 18 patients. The mechanics and farmers, of whom there were 15, outnumbered the groups of lawyers, of clergymen and of teachers.

In this presentation emphasis will be laid on the age at onset, age at death and duration of symptoms. The mean age at which pain first appeared was 57.5 years. The mean age at death was 63.3 years. Of greater interest than these averages is the distribution according to age groups, which is shown in Chart I. It will be seen that 65% did not develop pain until after 55. Of the entire group, 70% lived for 60 or more years. One patient, aged 47, had suffered from angina for only 4 months when he died from coronary thrombosis; the other extreme was a man who had angina for 24 years and died at the age of 82. The average duration of life for the whole series was 5.8 years; for those whose angina began between the ages of 45 and 74, the average was 6 years. The duration of life related to the age at onset is shown in Table 1, and in the bottom line of this table will be found the number of cases for each duration period. Fifty-four patients (32.5%) lived for 3 years or less. More detailed examination of this 3-year group is desirable and will help to explain the short duration of life of these people. Eighteen of these cases developed angina between the ages of 60 and 64, while 11 did not acquire the symptom until they had passed 65 years. Nineteen, or 36% of the 3-year group, suffered from essential hypertension, and 8 had hypertension of the arteriosclerotic type. There were serious complicating diseases in 6 patients, and also in this group were encountered 6 instances of excessive use of tobacco and alcohol. Those who died from disease other than cardiovascular, and those who suffered from essential hypertension, and those who did not develop angina until after 65 years accounted

for 64% of the 3-year group. There were apparently but 8 cases, 15% of the 3-year group and 4.8% of the entire series, who died from uncomplicated arteriosclerotic heart disease before 60 years of age. If this 3-year group be set aside there remain 112 cases, with an average duration of life of 7.7 years. In any consideration of prognosis there are two factors which must never be overlooked. The first concerns longevity itself, and of this it may be said that there is at present no reason to believe that the three score years and ten

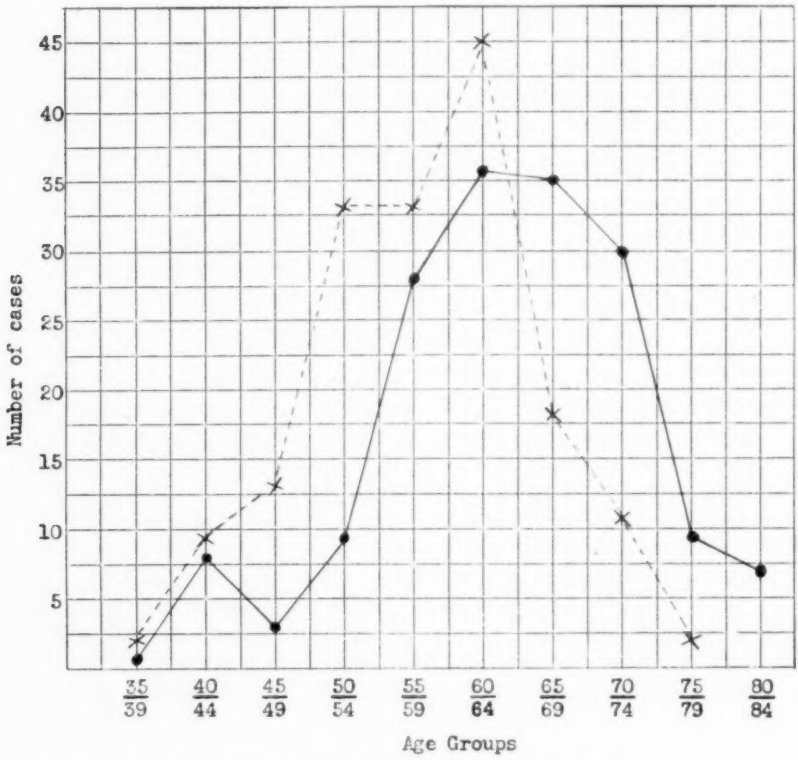

CHART I.—The distribution of 166 cases of angina pectoris according to age groups. Broken lines, age at onset; solid line, age at death.

allotted to man by the Psalmist will be extended. The available evidence rather indicates that the possible span of life by reduction on the final decades is shortening and not lengthening. The second factor is that of life expectancy, which at birth is now approximately 60 years, and is the greatest in recorded history. In this series, 30% of the patients died before 60; 70% reached or exceeded the present life expectancy, while 48% passed it by 5 or more years. It cannot be denied that the morbid process which underlies the

anginal syndrome does shorten life, and for the group of 112 patients, who began to suffer from angina at an average age of 57 years, there was a material reduction in the life expectancy estimated for that age. These people ought to have lived to an average age of 73.6 years. But by living to an average of 64.3 years they did complete 87% of the average lifetime of all persons who survive to the age of 57. One certainly would not attempt to minimize the seriousness of angina pectoris for the individual victim, but there is apparent in this disorder a striking disparity between the particular and the general. For the afflicted person the syndrome often constitutes a painful, even terrifying disease; it may cause serious limitation of activity, and for the individual the only thing

TABLE 1.—DURATION RELATED TO AGE AT ONSET.

Age at onset, yrs.	½	1	2	3	4	5	6	7	8	9	10	11	12	13	14	17	19	24	No. of cases	Av. for group
35–39	..	..	..	1	1	..	..	..	..	..	..	..	..	..	..	..	..	..	2	3.5
40–44	1	2	..	2	1	..	3	..	..	..	..	..	..	..	..	..	..	..	9	3.5
45–49	..	2	1	..	..	2	3	1	1	..	1	..	2	..	..	1	..	..	14	7.0
50–54	1	1	1	3	1	5	6	3	2	3	1	3	..	..	..	1	..	..	31	6.5
55–59	..	2	1	4	3	5	3	5	1	3	1	2	2	..	1	..	..	1	34	6.9
60–64	1	4	8	7	3	3	6	2	3	..	1	1	3	..	..	..	1	..	43	5.1
65–69	..	3	3	..	4	2	1	2	2	..	1	..	1	..	1	..	..	..	20	5.3
70–74	..	..	1	3	1	1	..	..	3	1	..	..	..	1	..	..	..	..	11	6.0
75–79	..	1	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2	2.0
No. of cases	3	15	15	21	14	18	22	13	12	7	5	6	8	1	2	2	1	1	166	5.8

certain about his prognosis is its uncertainty. But in its general aspect, when the anginal syndrome is viewed, not as it presents itself in an individual, but in a large group, and in the light of average duration of symptoms, age at onset and age at death, and is compared with life expectancy and possible length of life, then angina pectoris seems much less grave and it does not stand out as a serious complication of arteriosclerotic heart disease.

The influence on prognosis of variation from normal is difficult to estimate, but the fact that 50% of these patients had, as far as is known, normal blood pressure levels throughout their course suggests that hypertension is not a factor of primary importance. There were 36 examples of typical essential hypertension, and of

these, 53% lived for 3 years or less after the onset of angina; in this group essential hypertension represented the primary disease in which angina appeared as a late complication. Scattered cases occurred after the 3-year period, but it is by no means certain that in these patients hypertonus was continuous. There were 45 patients who had transient periods of hypertension, or hypertension of the arteriosclerotic type, with high pulse pressure. For a number of patients this type of hypertension did not appear until angina had been present for several years. This latter type of hypertension reached its maximum incidence in the 5-year duration period, after which it was less frequently encountered. It is of interest to note that 68% of the women had hypertension compared to 50% of the entire group, and that the average age at death for the women was 67.1 years, nearly 4 years beyond that of the group as a whole.

The simultaneous existence of complicating factors occurred in less than one-fifth of these patients. Even when these were such as to suggest some causal relation, it was not possible to evaluate their rôle in prognosis. There were 9 instances of diabetes mellitus. Malignancy, gastro-intestinal and pulmonary disease occurred infrequently. The low incidence of prostatism was rather striking. There were but 3 known cases of rheumatic heart disease and 3 cases of luetic infection. Excessive use of tobacco was noted 16 times; 6 of these patients were in the group that lived for 3 years or less. On the other hand, the patient who had angina for 24 years used tobacco liberally, and another who used tobacco to excess also had diabetes for 6 years and had borne his angina for 3 years, when he died from coronary thrombosis, but at the age of 76 years. However, one may question whether the low incidence of excessive use of tobacco in the entire group, less than 10%, and the unusually long duration of life with angina in the series are in any way related. Examples of obesity occurred in all groups and that state appears to have no bearing on prognosis. Seventeen patients had 19 surgical operations, 8 tonsillectomies and 11 major operations. There were 2 operative deaths, but whether or not these were of cardiac origin, cannot be stated. In general, it does not appear that angina pectoris by itself constitutes an undue risk if surgical intervention is indicated. Unfortunately, this study can throw no light on the effect on prognosis of adequate medical control of patients who have angina. A few examples suggest that the submission to supervision might in many instances prolong life. The most striking case in this series presented at the age of 51 years, in addition to effort angina of 2 years' standing, obesity, hypertonus, pulsus alternans, congestive failure, cardiac enlargement and an abnormal electrocardiogram, and yet this man lived for 9 years, when he died from coronary thrombosis. It is known that he lived very carefully during those years. Another man, a severe diabetic with angina, lived for 6 years during which he violated for much of the time all

the rules laid down for diabetes and heart disease; it seemed as though with reasonable care this patient might have gone on much longer. On the other hand, the case of shortest duration who died at 47 years had extensive coronary artery disease which was not even suspected until a few months before death and certainly could not have been influenced by any now known measures. From the study of this particular series the impression is gained that examples similar to the last cited are relatively uncommon and that cooperation of the patient with reasonable medical control is worthy of trial.

There were electrocardiograms for most patients and for a few interesting serial records. While at times helpful for diagnosis, it is quite certain that the standard lead electrocardiogram is of no value for prognosis. Inversion of T in Lead I seemed to be the abnormality most frequently associated with effort angina. As the cardiac lesion progressed inversion of T_2 appeared. There were numerous cases with a definite history of pain for 3 to 5 years before any abnormalities were recorded, and in one instance the electrocardiogram was still normal 13 years after the onset of angina. One patient had a normal electrocardiogram 3 days, and another 5 days before death from coronary thrombosis. In 3 cases there was T-wave inversion before the onset of angina. One patient had left axis deviation and deep inversion of T in the first lead 9 years before death occurred. Disturbances of rhythm other than premature beats were rare. There was one example of transient auricular fibrillation, one of permanent fibrillation (with mitral stenosis) and one of auricular flutter, which probably followed coronary thrombosis.

This series does not contain sufficient data for a satisfactory evaluation of the influence of heredity. The mean age at death of the patients was 63.3 years. For those known, the mean age at death of the fathers was 65.4 years, and for the mothers, 68.9. These are uncorrected figures and include such factors as early deaths of mothers from childbirth, and early death of either parent from acute infection or accidents. Cardiovascular disease was the cause of death for 37.5% of fathers, at a mean age of 64.5 years, and for 28.4% of mothers, at a mean age of 68 years. More mothers died from senility than from cardiovascular disease. There were several examples of patients who exceeded the span of their parents, who were likewise victims of cardiovascular disease. One does encounter families with a remarkable incidence of arteriosclerotic heart disease which may well be attributed to transmission from one parent, but such family histories are comparatively infrequent in this clinic. For this particular series of cases, when one considers the low familial incidence of cardiovascular disease and that duration of life of both patients and parents has exceeded their life expectancy at birth, heredity apparently is not an important

factor in prognosis, and from this study it is difficult to see how inherited defects in the vascular system can play a very large part in the present high incidence of arteriosclerotic heart disease.

Study of the causes of death in this series points to the high probability that a patient who has effort angina will die a cardiac death. For 15 patients nothing is known concerning the manner of death. Fifty patients died suddenly; the mechanism is not known in 16 of these. There were 87 deaths attributed to coronary thrombosis and 21 deaths from congestive heart failure; some of the latter may have been preceded by that accident, but this is not known. Thirteen deaths were ascribed to cerebral accidents. Thus, over 80% of the entire series died from cardiac or vascular disease. For the remainder the causes of death were variable and need not be enumerated; there were 3 suicides; other causes did not include more than 2 cases in any one group.

Summary. A study was made of 166 cases of effort angina, seen in a clinic in which arteriosclerotic heart disease is the predominant type. The influence of hypertension, obesity, familial vascular disease and certain miscellaneous factors has been considered. Electrocardiograms were available for most patients, but were found of no value for prognosis. Nearly one-third of these patients died suddenly, and over half died from coronary occlusion. Cardiac or vascular disease was responsible for death in over 80% of the series. The average duration of life in this series, 5.8 years, was greater than is usually anticipated. While prognosis in the individual case must always be uncertain, when viewed in the light of its comparatively long duration, and the late ages at onset and death, compared with life expectancy, the anginal syndrome appears less grave and does not stand out as a serious complication of arteriosclerotic heart disease, with which it is most commonly associated.

THE EFFECT OF BACTERIA ON THE NORMAL STOMACH AND ON ACUTE EXPERIMENTAL GASTRIC ULCER IN DOGS.*

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In a previous experimental study[1] on the production of gastric ulcer it was found that the gastric tissue showed a resistance to

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acids up to a certain strength. It was determined, for example, that ulcers could be produced in most instances by the injection of a 1% hydrochloric acid solution into the gastric tissue while the injection of lesser strengths of this acid produced inconstant results. These ulcers have a tendency to heal rapidly, usually within a period of 3 weeks. Chronic ulcers could not be produced by this method alone.

A review of the literature on this subject reveals many different opinions regarding the effect of bacteria in the production of chronicity of gastric ulceration. Since it has been maintained by many who have investigated this problem that chronic ulceration is due to, or augmented by, a secondary infection, we thought it advisable to bring the gastric mucosa and the acute ulcer into intimate contact with potent cultures of the common organisms.

Dogs were used in our experiments because we could easily produce acute ulcerations without disturbing the mucosa from within and without resorting to any major operative procedures. It is agreed by most observers that acute ulcers in healthy animals heal rapidly no matter how produced.

The Effect of Gastric Secretion Upon Bacteria. According to Bartle and Harkins,[2] gastric contents are by no means sterile. They have found that practically no germicidal value could be demonstrated at concentrations of free hydrochloric acid below 0.04%; but gastric juice containing from 0.08% upward had a well-marked bactericidal effect. Johnson and Arnold[3] found that the free acid gastric contents of dogs did not kill bacteria but exercised only a bacteriostatic influence on the flora. Knott,[4] on the other hand, has shown that free hydrochloric acid in a strength less than that found in the average normal stomach is sufficient to destroy many forms of bacteria, especially streptococci.

Van der Reis[5] dipped little cubes of bacon and apple seeds, to which threads were tied, into prodigiosus and staphylococcus cultures and had the patient swallow them. From these the bacteria could be cultivated when they were withdrawn 1 or 2 hours later.

Bartle reports that gastric juices from 10 to 20 degrees free hydrochloric acid were more germicidal for Streptococcus viridans and B. coli communis than for Staphylococcus aureus; the latter organism even in higher degrees of acidity showed considerable resistance.

Interestingly enough, Andrews and his coworkers[6] have demonstrated that bacteria already present locally in tissue can be made to multiply when the area is damaged in certain ways.

In our experiments we thought it best to administer the bacteria mixed with food in order (1) to dilute and neutralize the gastric contents, and (2) so that the bacteria would not only remain in the stomach for longer periods but would be protected from "acid" attack by their admixture with the food. We also administered

bacteria alone in one group of animals, and in another group we gave large amounts of sodium bicarbonate in order to neutralize the gastric acidity at the same time that the bacteria were in the stomach.

In another series of experiments we produced ulcerations in the stomach, by injection of hydrochloric acid into the gastric wall and fed the animals with bacteria alone and bacteria with the addition of sodium bicarbonate. The bacteria were of the following potency: Streptococcus, 1.5 billion per cc.; B. coli and staphylococcus, 5 billion per cc. The site of the injection had been marked with a bead.

The preliminary group of experiments are briefly recorded in Table 1.

TABLE 1.—EXPERIMENTS WITH NORMAL GASTRIC MUCOSA.

No. of dogs.	Time, days.	0.5 cc. culture injected into stomach wall (24-hr. broth)	Site of injection.	10 cc bacteria fed daily.	$NaHCO_3$ fed daily.	Mucosa at autopsy.	Remarks.
2	18	Staph. aureus	Lesser curva.	None	None	Normal	
2	20	Staph. aureus	Lesser curva.	Staph. aureus	None	Normal.	
2	6 20	Staph. aureus	Lesser curva.	Staph. aureus	1 ounce	Normal.	
2	30	S. viridans	Lesser curva.	None	None	Normal.	
2	28	S. viridans	Lesser curva.	S. viridans	None	Normal.	
2	28	S. viridans	Lesser curva.	S. viridans	1 ounce	Normal.	
1	30	None	None	S. viridans	None	Normal	Control.
2	57	B. coli	Lesser curva.	None	None	Normal.	
1	25	B. coli	Lesser curva.	B. coli	None	Normal.	
2	25	B. coli	Lesser curva.	B. coli	1 ounce	Normal.	

It is interesting to note that Best and Orator[7] injected into the stomach wall of rabbits 2 cc. of a $\frac{1}{100}$ Staphylococcus aureus (24-hour) culture. All of their animals died within 48 hours and yet the pathologic picture at autopsy was quite innocent.

Our work recorded in Table 1 on S. viridans is confirmed by Türck,[8] who injected streptococci into the mucosa of the stomach with negative results. He also fed large amounts of streptococci (and B. coli communis, separately) which were given daily at a time when the stomach was empty to dogs in which an experimental abrasion was made in the pyloric and duodenal mucosæ with negative results. These findings were also confirmed by Wilensky and Geist.[9]

Saunders, Holsinger and Cooper[10] infected threads with a streptococcus isolated from resected peptic ulcers and inserted them into the wall of the stomach and duodenum, the thread passing through all three layers. Sections failed to show tissue changes microscopically. Our observations are in accord with the latter findings.

The Production of Gastric Ulceration by Hydrochloric Acid. In a previous communication[1] it had been shown that a 1% solution of hydrochloric acid produced an acute ulcer very constantly. These ulcers healed completely within a period of 7 to 21 days. In the

present experiments it was believed that the acute ulcers could be infected and in that manner become chronic. Ulcers were produced by the injection of 1% hydrochloric acid. Feedings with different bacteria, such as Staph. aureus, B. coli and S. viridans, potent enough to produce secondary infection of the ulcer, was instituted. The following experiments were carried out after the acute gastric ulceration had fully developed (Table 2).

TABLE 2.—EXPERIMENTS WITH MUCOSA WITH ACUTE GASTRIC ULCER PRODUCED BY HYDROCHLORIC ACID.

No. of dogs	Time, days	10 cc. bacteria fed daily	$NaHCO_3$ fed daily	Autopsy findings	Remarks
1	35	Staph. aureus	None	Definitely healed ulcer	Rugæ converged toward ulcer.
2	49	Staph. aureus	None	Definitely healed ulcer	Rugæ converged toward ulcer.
1	8	Staph. aureus	1 ounce	Deep ulcer	Elevated round edges—characteristic of indurated ulcer.
1	9	Staph. aureus	1 ounce	Perforating ulcer	Characteristics of acute ulcer.
2	19	Staph. aureus	1 ounce	Definite ulcer.	
1	49	Staph. aureus	1 ounce	Completely healed ulcer.	
2	21	S. viridans	None	No ulcer.	
2	21	S. viridans	1 ounce	Definite healing ulcers.	
1	35	B. coli	None	Definite healed ulcer.	
2	44	B. coli	None	Healed ulcer in 1; normal mucosa in other.	
1	3	B. coli	1 ounce	Perforated ulcer.	
1	12	B. coli	1 ounce	Perforated ulcer.	
1	15	B. coli	1 ounce	Small ulcer.	
1	27	B. coli	1 ounce	No ulcer.	

As a separate study the following experiments were performed: 0.5 cc. of 1% hydrochloric acid was injected through the serosa into the muscular walls of the stomachs of 3 dogs. Three days later, after the production of necrotic ulcers, 1 cc. of S. viridans (24-hour broth culture) was injected in each dog through the serosa into the muscular and submucosal areas surrounding the ulcers. In 1 of these dogs a healed ulcer was found after 34 days; in another, sacrificed 54 days after production of the ulcer, examination of the stomach showed an old healing perforated ulceration with the rugæ converging toward the ulcer, the base of which measured 2 mm. The third dog was sacrificed 57 days after ulcer production and no sign of ulceration could be discovered.

The same study was repeated except that gastrostomies were performed in order to visualize the ulcers and, therefore, to allow direct injections of bacteria into their walls from the mucosal side of the stomach. Four dogs had ulcers produced by injection of 1% hydrochloric acid. Three days later gastrostomies showed

definite ulcerations in each instance; 1 was actually perforated but was sealed off by omentum. The immediate area surrounding each ulcer was inoculated directly through the mucosa with 1 cc. of a 24-hour culture of S. viridans. The gastrostomy was closed in each instance. Two dogs were examined 59 days after ulcer production and both showed complete healing. There was some induration of the gastric wall in both cases (1 of these had perforated). In the other 2 animals the ulcers were also healed, but in 1 the gastric wall was perfectly normal; in the other there was only the slightest induration.

Soda Controls. In 2 dogs in which ulcers were produced by the injection of 1% hydrochloric acid, soda alone was given by mouth for 88 days. They were sacrificed and both revealed definite healed ulcers. In 2 other dogs in which soda was fed without the production of the acid ulcer, 1, after 19 days, revealed no gastric changes and in the other, after 88 days, the mucosa was normal.

Microscopic studies made of the gastric tissue surrounding the areas of injection of colon, streptococcus and staphylococcus bacteria revealed the following data: The mucosa was essentially normal; the submucosa in most instances revealed a slight edema and round-cell infiltration. In 1 instance a thrombotic vessel and in another a submucosal infarct were found. The muscularis was normal in most instances, but in 1 an area of necrosis and in another a slight infiltration of round cells were found. The serosa, in a few instances, showed evidences of localized peritonitis, and in 1 instance there were many small localized abscesses (staphylococcus). Although there were slight microscopic changes, the macroscopic appearances were entirely normal.

Test meals were made in a number of the dogs but the results obtained were not significant. The gastric contents were cultured in 5 instances with negative results. Blood cultures were made in 3 instances with negative results. In a few of the dogs fed with soda, CO_2-combining power determinations of the blood were made and these also proved to be normal. Blood counts were normal in the 8 animals in which they were done.

Summary. Gastric ulceration has been regarded as due to a bacterial invasion of the gastric mucosa, the chronicity of ulcers being maintained by the infection. Other observers have stated that the chronicity of ulcers is dependent upon the effect of hydrochloric acid irritation. The consensus of opinion is that both factors are important in the chronicity of gastric ulceration and, since hydrochloric acid of normal strength fed to dogs does not produce a chronic ulcer, it would follow that if this view is correct the factor of bacterial infection might be of paramount importance.

The present experimental study deals with the effect of bacteria upon the normal gastric mucosa and upon the mucosa with acute gastric ulceration produced by hydrochloric acid. It was found that large amounts of bacteria mixed with food did not produce

ulceration nor mucosal irritation when fed to dogs. When bacteria were fed to dogs in which acute gastric ulceration had been produced by hydrochloric acid, no infection of the ulcer took place and chronicity was not noted, the ulcer healing completely, though in some cases in slightly prolonged time. Even after giving large amounts of sodium bicarbonate, the bacteria had no permanent effect upon the gastric mucosa or the acute ulcers.

After potent cultures of bacteria are injected into the gastric wall, infection with consequent abscess formation and necrosis does not generally take place in the dog's stomach.

In several instances gastrostomies, permitting direct inoculation of the ulcer walls with S. viridans, did not prevent rapid and complete healing of what were observed to be deep necrotic (in 1 instance, a perforated) ulcers.

The acute hydrochloric acid ulcer is a clean-cut, non-infected, necrotic ulcer which apparently does not lend itself to bacterial infection.

Chronic gastric ulceration cannot be produced by bacteria alone or by bacteria acting on acute hydrochloric acid ulcers, at least in the dog. It seems that another factor must play an important rôle in its chronicity.

The high acidity of the dog's gastric contents seems to inhibit the growth of bacteria; but this hardly explains the results obtained after neutralizing the gastric contents with food and alkalies given simultaneously with the bacteria.

The authors wish to thank Dr. Frank W. Hachtel, Professor of Bacteriology, University of Maryland Medical School, for his assistance in these studies.

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BLOOD GLUCOSE CLEARANCE.

ITS DETERMINATION BY A MICROINTERVAL METHOD.

I. STUDIES IN NORMAL AND DIABETIC PERSONS.*†

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SINCE 1913 a vast literature has accumulated on the use of glucose tolerance tests as diagnostic and prognostic aids in diabetes mellitus, various endocrinal and nervous diseases, arthritis, carcinoma and many other diseases. Classified according to the route of administration of the glucose, these tests have been of two main types: the oral and the intravenous. The literature on the oral glucose tolerance test has been reviewed recently.[1] The inconsistencies of the test have been reëmphasized and explained by irregularities in gastric emptying. Work demonstrating marked variations in gastric evacuation in normal individuals and corresponding changes in the blood sugar curves has been cited.

To eliminate errors arising from differences in absorption, intravenous glucose tolerance tests have been devised. One of the earliest and still the most accurate of these was introduced by Woodyatt, Sansum and Wilder,[2] but the expense of the apparatus used and the length of time required for the test have made it impractical for routine use.

Other intravenous glucose tolerance tests have been carried out according to the following general plan: A quantity of glucose greater than the body can immediately dispose of is injected intravenously in a short period of time. Blood specimens are taken at fixed intervals thereafter and the tolerance is determined by the height to which the blood sugar rises and the time required for it to return to normal.

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The 23 tests of this type which we have found in the literature since 1913[3] differ widely in technical details but in our opinion have certain faults in common.

1. *Dosage.* In 17 of these tests, identical amounts of glucose were given to different patients regardless of body weight. In 1 of these, for instance (Jorgenson and Plum), the routine dose of 20 gm., when calculated in terms of body weight, gives amounts varying from 0.18 to 0.66 gm. per kg. These authors contended that the weight factor was unimportant. Yet in our experience, varying the dosage from 0.1 to 0.33 gm. per kg. results in corresponding changes in the height and duration of the curves, as illustrated in Chart 2.

2. *Injection Time.* In 7 of these tests the time allotted to the administration of glucose was not uniform; in 4 others it was not mentioned. We have found pronounced differences in duplicate curves when the injection time was increased from ½ to 1½ minutes with an otherwise constant technique and, therefore, feel that it is a factor warranting standardization.

3. *Number of Blood Specimens and Intervals of Collection.* In 22 of the 23 intravenous tests, collection of blood samples covered a period of 1 to 4 hours and necessitated several venous or capillary punctures. The discomfort incident to multiple punctures and the time consumed in carrying out these tests are serious drawbacks from the standpoint of both patient and laboratory.

The Microinterval Technique. *General Remarks.* In the modification to be offered in this presentation, an effort has been made to eliminate the undesirable features of other intravenous tests. For reasons stated above, the dosage of glucose was based on body weight.* A dose of 0.2 gm. per kg. was chosen because it produced a curve whose blood sugar range closely approximated that obtained by the more familiar oral technique.

For comparable results, a uniform injection time is obligatory, and a period of 1½ minutes was chosen because it was most convenient for the quantities given.

Since a complete "arm to arm" circuit of the blood is made every 20 to 30 seconds,[4] it seemed reasonable to expect a distinctive response in normals and diabetics within a very few minutes after the injection of glucose. Klein and Holzer,[3] taking specimens at 30-second intervals, found definite differences in the curves of normals and diabetics within 6 minutes. Since their method involves puncture of the radial artery, it is not practical as a clinical test.

* A tendency toward "diabetic curves" was found in obese subjects showing no clinical evidence of diabetes mellitus. It is probable that in this type of individual it would have been more accurate to have based the dosage on surface area rather than body weight, since the mass of active protoplasm is more nearly proportionate to the former.

By the use of a three-way stopcock between needle and syringe, it was possible to collect venous specimens at any desired time during a period of 15 minutes with but one insertion of the needle. At first specimens were taken 1, 2, 3, 4, 5, 6, 7, 10, 15 and 30 minutes after the completion of the glucose injection. The 1- and 2-minute readings were generally on the ascending limb of the curve, were not particularly informatory and, therefore, were discarded. The *peak point* (highest reading) occurred between the 3d and 5th minute after the end of the injection and was clearly shown in samples collected every 60 seconds during this period. (Fifteen-second intervals were tried in a few cases but greatly increased the technical work and were of no apparent additional diagnostic value.) The descending limb of the curve was adequately shown by specimens at 5, 10 and 15 minutes. Although the blood sugar at the latter time was still above fasting level, little additional information was gained by prolonging the test to 30 minutes, since this phase of the curve was relatively asymptotic.

Procedure. At the risk of making the mechanics of the test seem cumbersome, the technique which we have used is described in detail.

The following material is needed: One 50-cc. syringe, graduated in units of 1 cc.; 2 three-way metal stopcocks; 2 18- or 19-gauge intravenous needles; 1 ampule of 50% glucose;* 4 to 6 5- or 10-cc. syringes; oxalated test tubes; watch with second hand.

The patient, previously on a mixed diet, is directed to eat nothing after 6 o'clock on the evening before and to report at the laboratory between 8 and 9 o'clock the following morning. Fifty per cent glucose is drawn up into the large syringe to the amount of 0.2 gm. per kg. body weight, the three-way stopcock and needle attached and a vein in the antecubital fossa is entered with the valve so set that the blood flows through the side arm into an oxalated tube. After the fasting specimen has been collected, the tourniquet is released, the valve turned so that the needle and syringe are connected and the injection is started. While the injection is in progress, an assistant calls off 15-second intervals by the watch. One-sixth of the total amount of glucose is given during each 15-second period and the injection is finished in exactly $1\frac{1}{2}$ minutes. Within the next $2\frac{1}{2}$ minutes a tourniquet is applied to the opposite arm, a small syringe and three-way stopcock fitted to the other needle and a vein entered. The tourniquet is then removed and discarded and the needle is left *in situ* for the remainder of the test. Two- to 4-cc. blood samples are collected exactly 3, 4, 5, 10 and 15 minutes after the end of the injection.

After each specimen has been collected, the valve is turned so that syringe and side arm are connected, the syringe detached and replaced by a clean dry one. With each change of syringe, air is forced through the stopcock so that residual blood is ejected through the side arm. In the intervals between the last 3 specimens, the valve is so set that the needle and syringe are connected and sufficient suction is applied to remove 1 or 2 cc. of blood per minute. This is merely an additional precaution to prevent clotting and the blood so obtained is discarded.

* Commercial ampules of 50% glucose were used, largely for the sake of convenience. The product used was analyzed for glucose by the Folin-Wu method, and the concentration was found to be as stated. It is, therefore, probable that errors arising through reliance upon commercially prepared glucose solutions are negligible.

After a few tests have been done, there is seldom any difficulty in obtaining the specimens in the manner given above. Two persons are needed to perform the test—one to insert the needles, give the glucose and take the samples—the other to keep the time, transfer the specimens into test tubes, oxalate the blood and rinse and dry the syringes.

For blood sugar estimations, the Folin-Wu method* has been used.

Nomenclature. Since this test is a measure of the rapidity of the disappearance of injected glucose from the blood stream, it will be referred to as the *microinterval glucose clearance test.*

Results. *Results in Normal and Diabetic Persons.* The fasting, peak and 15-minute blood sugar levels in 65 metabolically normal individuals and 113 cases of diabetes mellitus are plotted in Chart 1. (Thirty-two of the latter were controlled on diets containing 150 gm. or more of available glucose without insulin.) The classification as "normal" or "diabetic" was made only after careful and generally prolonged clinical observation.

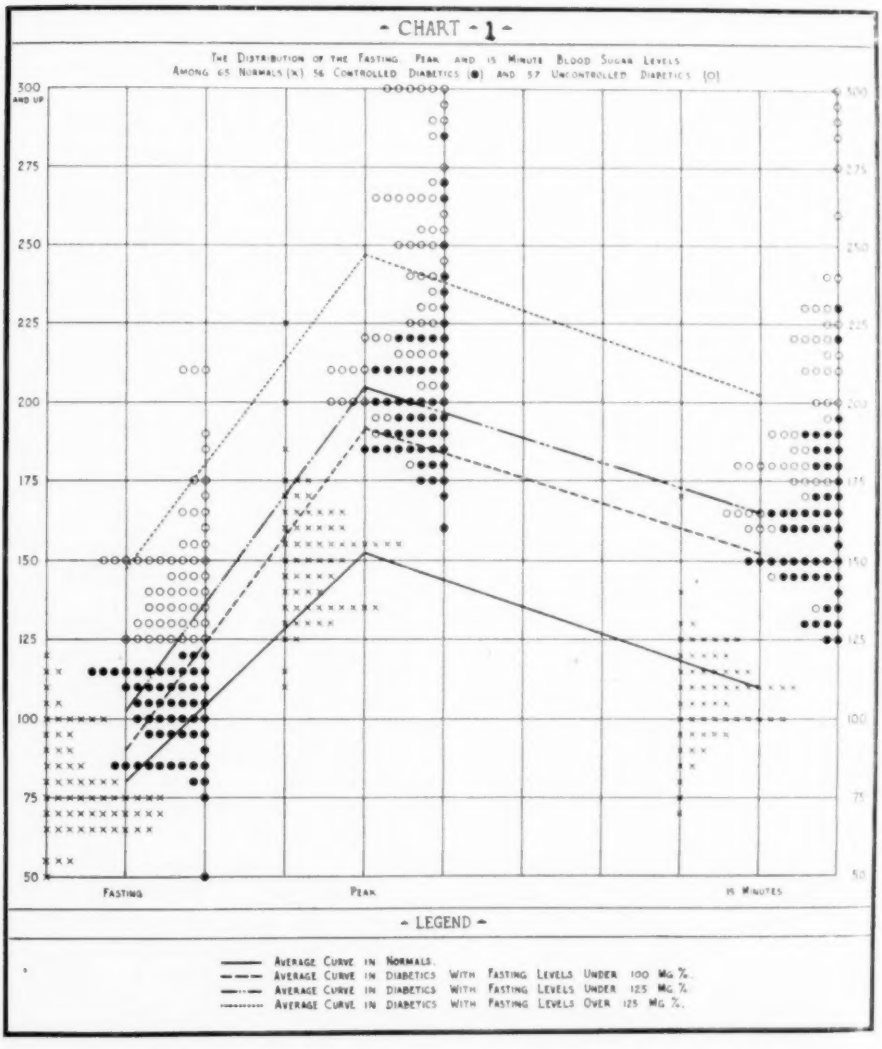
The most important diagnostic criteria of the curve obtained by the microinterval technique are: (1) the height of the "peak point," and (2) the 15-minute blood sugar level. The peak of the blood sugar curve was 175 mg.% or below in all but 3 of the "normals." One of these had a fractured femur, another a sciatic neuritis. The third had a pronounced psychoneurosis and showed a normal curve on repetition of the test. The 15-minute level was 125 mg.% or below in all but 4 of the normals. Two of these corresponded to the first 2 mentioned above, the third had migraine and the fourth was apparently healthy. Only 2 diabetics—both extremely mild—had peaks below 175 mg.% and none was below 125 mg.% at 15 minutes. Two diabetics (1 of whom had a low peak) had "borderline" 15-minute levels of 125 mg.% and 3 more had "borderline" peaks of 175 mg.%.

A diagnostic point of minor significance is the time at which the apex of the curve is reached. Fifty seven per cent of the normal and but 45% of the diabetic, group attained the peak by the 3d minute, the more severe the diabetes, the greater being the tendency toward a delayed peak.

In computing average curves, the diabetics have been divided into 3 groups: (1) Those with fasting blood sugars below 0.1%; (2) those with fasting levels below 0.125%; (3) those above 0.125% (Chart 1). The average fasting blood sugar of the 20 diabetics in Group 1 was only 5 mg.% higher than the mean initial level of the group of normals, whereas the average peak and 15-minute readings of the diabetics exceeded those of the normal by 39 and

* That this method of blood analysis does not give true sugar values is of little importance, since the non-sugar reducing substances are constant and hence do not alter the shape of the curve. That this method is inaccurate with very high or very low blood sugars is likewise of little consequence in this test, since most of the readings are between 0.070% and 0.22%. In 59 duplicate determinations an average difference of 3.4 mg.%, and a maximal difference of 13 mg.%, in the two analyses were found.

44 mg.%, respectively. The composite curve of the diabetics of Group 2 exceeded that of the normals by 21 mg.% at the fasting level, 53 mg.% at the peak and 55 mg.% at 15 minutes. Thus it is evident that differences in the microinterval glucose clearance


- CHART - 1 -
THE DISTRIBUTION OF THE FASTING, PEAK AND 15 MINUTE BLOOD SUGAR LEVELS
AMONG 65 NORMALS (X) 56 CONTROLLED DIABETICS (●) AND 57 UNCONTROLLED DIABETICS (O)
300 AND UP
275
250
225
200
175
150
125
100
75
50
FASTING
PEAK
15 MINUTES
- LEGEND -
AVERAGE CURVE IN NORMALS.
AVERAGE CURVE IN DIABETICS WITH FASTING LEVELS UNDER 100 MG %.
AVERAGE CURVE IN DIABETICS WITH FASTING LEVELS UNDER 125 MG %.
AVERAGE CURVE IN DIABETICS WITH FASTING LEVELS OVER 125 MG %.

curves of normals and diabetics are not merely reflections of differences already existent in the fasting levels.

Abnormal curves have been found in several conditions in which there was no clinical evidence of a coëxisting diabetes. Among these are cardiac decompensation with edema, hypertension, chole-

cystitis, peptic ulcer, hypopituitarism and chronic encephalitis, the curves of which will be presented and discussed in a subsequent communication.

Hence the microinterval intravenous method, like the oral test, is not specific for diabetes mellitus. The distinctive behavior of the diabetic as compared with the normal individual is quantitative rather than qualitative, and yet it is sufficiently striking in most cases to be diagnostic. A smaller dose of glucose (*e. g.*, 0.15 gm. per kg.) or calculation of the glucose dosage on the basis of surface area rather than body weight may diminish the number of "borderline" curves.

Sources of Error. 1. Dilution factor: In 15 cases, hemoglobin estimations (Sahli method) were made on each of the samples collected. The maximal dilution almost invariably occurred between the 4th and 6th minute, and in 13 of the 15 cases it ranged between 5.8% and 10% of the initial level. A case of polycystic kidney disease showed a 11.7% fall in hemoglobin, a case of polycythemia and hypertension, a 15.6% drop. Thus in the small series the error introduced through variations in the degree of dilution was generally less than 4% but in extremes was as high as 10%.

2. To investigate the possibility of an alteration in the flow of blood through the vein, due to the presence of the needle, a vein in the opposite arm was entered without applying a tourniquet and a specimen was taken simultaneously with one of those routinely collected during the course of the test. In 9 cases the average differences between the blood sugar readings in the 2 specimens was 2 mg.%, the maximal differences 6 mg.%, figures well within the limits of error of the Folin-Wu method of analysis. Since the results in these 9 cases so uniformly indicated that the needle did not interfere with the flow of blood through the vein, the series was not extended.

3. If glycogenolysis should occur in the liver during the course of the test, a serious error would result from the glucose liberated. Release of liver glycogen may well result from blood loss or from strong emotional stimuli. Since there was no appreciate change in blood sugar when specimens were taken in a similar manner after an injection of saline or alanin, the blood loss, in itself, is insufficient to provoke a hyperglycemia. Two patients were observed whose emotional state apparently affected the glucose clearance test. Both were very apprehensive and excited at the first test but placid at the second and showed high curves at the first test and normal ones on repetition. It is possible that undetected or less intense emotional stimuli affected the curves of many others to a lesser degree. If this were so, one would expect to find abnormal curves frequently in conditions characterized by emotional lability. In this connection, it is significant that 18 out of the 19 cases of hyperthyroidism had normal curves before operation

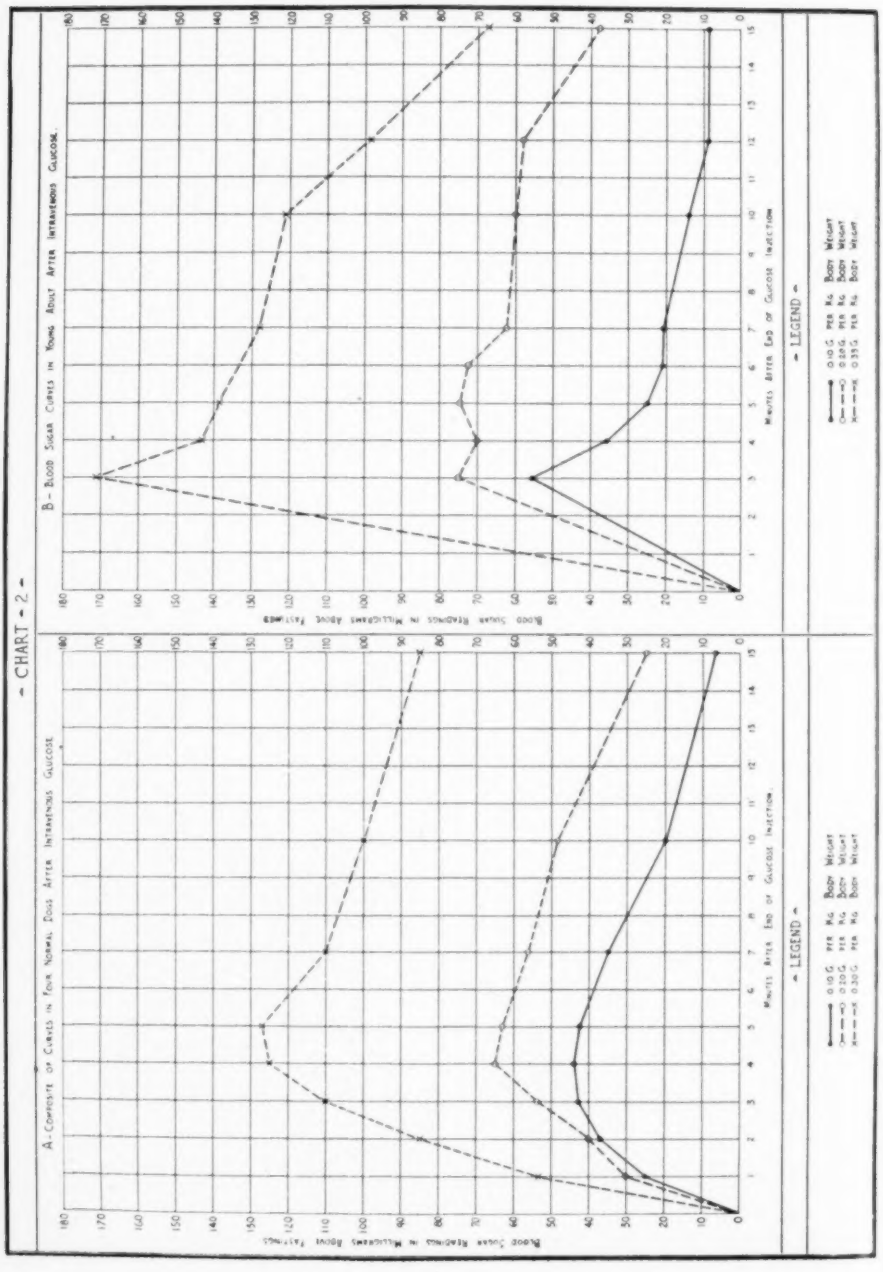


CHART 2
A.-Composite of Curves in Four Normal Dogs After Intravenous Glucose
B.-Blood Sugar Curves in Young Adult After Intravenous Glucose.
Blood Sugar Readings in Milligrams Above Fasting
Minutes After End of Glucose Injection
LEGEND
0.10 G. per Kg. Body Weight
0.20 G. per Kg. Body Weight
0.35 G. per Kg. Body Weight

and 6 out of 7 in whom the test was repeated postoperatively showed curves almost identical with those obtained beforehand. The only exception showed a higher curve after than before operation.

Comments. *Comparisons of the Oral and Microinterval Intravenous Tests.* The advantages and disadvantages of the oral and microinterval intravenous tests have been summarized in Table 1.

TABLE 1.—COMPARISON OF THE MICROINTERVAL INTRAVENOUS AND THE ORAL GLUCOSE TOLERANCE TESTS.

Criteria.	*I.V. Test.*	*Oral Test.*
Amount of glucose given	10 to 20 gm.	50 to 150 gm.
Effect on diabetic status	None demonstrable	Occasionally upsets tolerance seriously.
Time required for test	17 min.	2 to 4 hrs.
No. of venepunctures	2	3 to 5 or more.
	Rate of injection uniform	Rate of intestinal absorption indeterminate.
Technical difficulties	A good vein in each arm necessary—2 workers needed—experience with test required	None except venepuncture.
Value in the differentiation of normals and diabetics	Less overlapping in the curves of normals and mild diabetics with the intravenous than with the oral test.	
Agreement in repeated curves	Closer agreement in duplicate curves obtained by the I.V. method.	
Effect of previous diet	None demonstrated	Pronounced.
Background	Unphysiologic	Physiologic.
Functions involved	Principally diffusion through capillary walls (?)	Sum total of gastric emptying, intestinal absorption, diffusion and oxidation of glucose and conversion into glycogen.

Lennox[3] compared the oral and intravenous tests in a considerable series and concluded that the curves obtained by the intravenous method "exhibit less variation from subject to subject and in the same subject less variation from time to time."

To test this point in regard to the method under discussion, 2 or more intravenous tests were made on a group of 31 non-diabetic individuals. In Chart 3, the differences in blood sugars at coincident points in the curves of each patient have been compared with those found by Lennox[3] in duplicate curves by the oral method.* It would appear from these figures that repeated microinterval intravenous tests in the non-diabetic are in closer agreement than repeated oral tests.

Gray[6] warned of the danger of upsetting carbohydrate tolerance by the large doses of glucose generally given in the oral method. Beardwood's patient,[7] who was well controlled by diet alone before the oral test was carried out, showed a hyperglycemia and glycosuria on the same diet for 4 months afterward and for a time required 25 units of insulin daily. Many other examples of this situation

* The curves of 2 patients who were very apprehensive during the first test were excluded from Charts 1 and 3.

could be added by those who have used oral glucose tolerance tests in diabetic individuals. The chief experimental evidence in support of these clinical observations lies in the work of Allen[8] on the

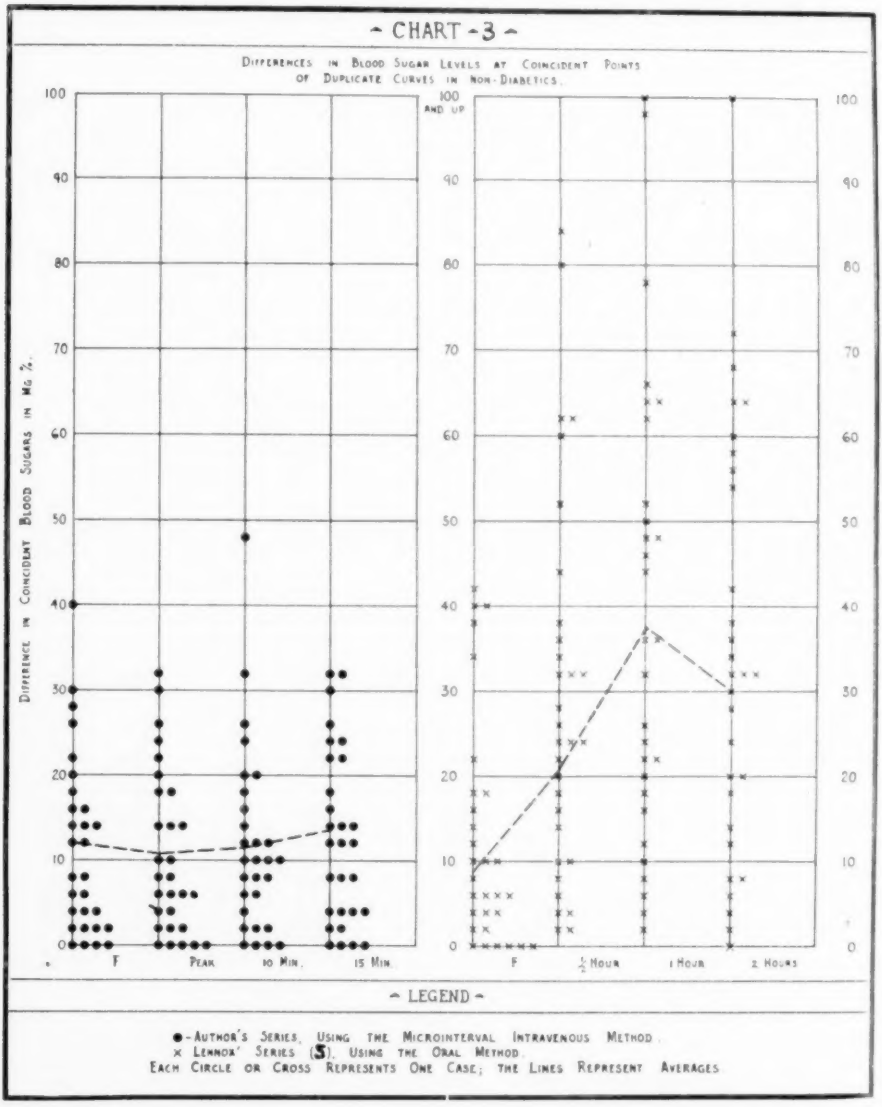


CHART 3
DIFFERENCES IN BLOOD SUGAR LEVELS AT COINCIDENT POINTS OF DUPLICATE CURVES IN NON-DIABETICS.
DIFFERENCE IN COINCIDENT BLOOD SUGARS IN MG %.
100 AND UP
F
PEAK
10 MIN.
15 MIN.
½ HOUR
1 HOUR
2 HOURS
LEGEND
●-AUTHOR'S SERIES, USING THE MICROINTERVAL INTRAVENOUS METHOD.
× LENNOX' SERIES (S), USING THE ORAL METHOD.
EACH CIRCLE OR CROSS REPRESENTS ONE CASE; THE LINES REPRESENT AVERAGES.

partially depancreatized dog. We have in no case observed reactions nor impairment of tolerance attributable to the glucose injected in the microinterval test.

Though the intravenous method for determining glucose tolerance is admittedly unphysiological, there is evidence to show that the passage of glucose through the liver prior to its entrance into the general systemic circuit makes little difference in the resultant blood sugar curves. McLeod and Pearce[9] injected glucose at a uniform rate into the superior mesenteric vein of dogs, took simultaneous specimens from the portal vein and inferior vena cava and found parallel curves after the first 2 minutes. Grafe and Meythaler[10] injected 5 cc. of 60% glucose into the femoral artery and into either the portal vein, hepatic or splenic arteries of the same dog on different days but under otherwise similar conditions. They took specimens from the ear capillaries and obtained closely comparable curves.

Fate of the Injected Glucose. The curves obtained by the microinterval method furnish an additional example of the rapid disappearance of intravenously injected glucose from the circulation. If the vascular system were impermeable to glucose, the injection of 0.2 gm. per kilo would raise the blood sugar from a fasting level of 0.1 mg.% to a plateau at 0.35 to 0.375 mg.%. Since the blood sugar generally does not rise above 175 mg.% in the normal and approaches the fasting level within 15 minutes, one may infer that the removal of the injected glucose begins at once and is almost complete in 15 minutes.

The following explanations for the disappearance of the injected glucose have been offered: (1) Conversion in the blood stream into a non-reducing substance; (2) excretion in the urine; (3) simple diffusion into the tissues; (4) conversion into glycogen; (5) oxidation.

1. By determining the total carbon content of the blood before and 2 minutes after the intravenous injection of glucose, Kurokawa[11] proved that the glucose did not remain in the blood stream in a non-reducing form but actually escaped into the tissues.

2. Though not routine, a sufficient number of urine examinations have been made during the course of the microinterval test to show that glycosuria is absent or negligible in normal individuals.

3. Most workers have attributed the rapid disappearance of glucose from the blood stream to simple diffusion into the tissues. Palmer[12] and Folin, Trimble and Newman[13] have found a substantial increase in the sugar content of various tissues, particularly the skin, shortly after the intravenous injection of glucose. Urbach and Sicher[14] and Trimble and Carey[15] found that the skin sugar concentration in relation to the blood sugar was appreciably higher in fasting diabetics than in fasting normals. Thus one might infer that, due to its higher sugar concentration, diabetic skin (and probably other tissues as well) may be less capable of removing added sugar from the blood stream than normal skin. Though differences in the gradient of diffusion may partially, if not wholly, account for the immediate divergence in the curves of normals

and diabetics, it seems unlikely that they are alone responsible for the differences in the latter parts of the curves.

4. There is as yet no analytical method sufficiently sensitive to be applicable to the study of the changes in tissue glycogen in the first 15 minutes after the injection of the relatively small amount of glucose used in this test.

5. Oxidation of glucose in the tissues has been studied by changes in the respiratory quotient. Since fluctuations in the respiratory quotient occur in fasting individuals and since a slight rise may be caused even by the act of drinking, changes of less than 0.05 have not been considered significant. Many workers[16] have found the first significant rise in R.Q. from 30 to 60 minutes after the oral administration of glucose. Similar results after intravenous injection were obtained by Bernstein and Falta[17] in man and by Ritlop[18] in dogs. Thus we may conclude that oxidation of glucose in the tissues is not demonstrable by present methods during the first 15 minutes after its administration.

There is evidence to show that administration of insulin prior to the injection of glucose expedites both the rise in R.Q. and the disappearance of the glucose from the blood stream. Ritlop found a much earlier response of the respiratory quotient to injected glucose when insulin was given prior to the glucose. Elias, Guedemann and Roubitschek[3] made duplicate intravenous tests in one of which 5 units of insulin were given 45 minutes before the glucose. The fasting level was not appreciably changed by the preliminary dose of insulin but the peak attained 5 minutes after the glucose injection was distinctly lower and the return to the fasting level more rapid.

Increased insulin activity is demonstrable in the blood in the pancreatic vein soon after the intravenous injection of glucose. Zunz and LaBarre[19] transfused blood from the pancreatic vein of 1 dog into the jugular vein of another for a period of 20 to 30 minutes and found no change in the blood sugar of the recipient. They then injected 60 cc. of 20% glucose intravenously into the donor during the blood transfusion and found a marked fall in the blood sugar of the recipient at the end of the transfusion. In a control experiment with the vagi of the donor severed, no change occurred in the blood sugar of the recipient.

Whether insulin is liberated rapidly enough from the pancreas to appreciably influence the disposal of glucose during the first 15 minutes after sugar injection is still a matter for conjecture. Reasoning from this premise, however, one might explain some of the differences between the normal and diabetic curves by the presence of an intact or impaired islet function.

Summary. Twenty-four intravenous glucose tolerance tests have been collected from the literature of the past 20 years and constructively criticized. A modification has been offered which is carried out, in brief, as follows: A vein is entered, a fasting speci-

men taken and glucose to the amount of 0.2 gm. per kg. body weight is injected at a uniform rate in exactly 1½ minutes. Within the next 3 minutes a vein in the opposite arm is entered and specimens are collected exactly 3, 4, 5, 10 and 15 minutes after the end of the injection. Since this test is primarily a measure of the rapidity of disappearance of injected glucose from the blood stream, it is referred to as the *microinterval glucose clearance test.*

In comparison with the oral and most of the intravenous tests, the method proposed in this communication has the following advantages: (1) A uniform rate of introduction of glucose into the blood stream is assured; (2) only 2 venepunctures are required; (3) the test is completed in 17 minutes; (4) a smaller amount of glucose is used; (5) repeated tests on the same individual are in closer agreement.

The results in 65 normal individuals and 113 cases of diabetes mellitus are presented. The most important diagnostic criteria of the curve are the height of the peak point and the 15-minute blood sugar level. The apex of the blood sugar curve was 175 mg.% or below in all but 3 of the normal group and the 15-minute level was 125 mg.% or below in all but 4 normals. Only 2 diabetics—both extremely mild—had peaks below 175 mg.% and none was below 125 mg.% at 15 minutes. In 2 diabetics, however, the 15-minute reading was exactly 125 mg.% and in 3 others "borderline" peaks of 175 mg.% were obtained.

We feel that a "normal" microinterval curve (peak of 175 mg.% or below and 15-minute level of 125 mg.% or below) is strong presumptive evidence against the presence of diabetes mellitus. On the other hand, an abnormal curve is not of equal diagnostic significance. Curves similar to those obtained in diabetes have been found in several other conditions, such as cardiac decompensation, hypertension, cholecystitis, peptic ulcer, carcinoma and chronic encephalitis.

The fate of the injected glucose has been conjectured and an attempt has been made to explain the early appearance of a distinctive response in normals and diabetics.

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(Titles have been omitted for sake of brevity.)

THOMSEN'S DISEASE.

(MYOTONIA CONGENITA.)

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CONGENITAL myotonia was first adequately described (1875) by J. Thomsen,[1] a Danish physician, himself a sufferer from the disease, and in whose family the disease was noted for five generations. It

had been observed previously by Bell (1832), Benedikt (1864), and von Leyden (1866). The name of myotonia congenita was attached to the disorder by Strümpell. Jelliffe and Ziegler[2] have recently reviewed 20 cases of congenital myotonia which had appeared in the American literature up to 1932.

The disease usually appears in several members of a family in successive generations. In most of the recorded cases, it has existed in several relatives of the patient, generally in one of the parents, and in the patient's brothers, sisters, and children. Many of Thomsen's ancestors are said to have suffered from mental weakness.

It appears in both sexes, but more commonly in the male. Koch[3] found 91 of 102 collected cases to be in men. Symptoms are noticed very early in life, and the disease tends to persist with varying intensity throughout life. When the patients are first seen, they are usually about 20 years old, or less, and have had the disease as long as they can remember; or, it may have been first noticed in childhood when athletic activity was restricted because of muscular stiffness.

The main features are a disturbance of muscular activity such that at the beginning of a voluntary movement excessive tonus of the muscles involved renders the movement slow and difficult. When a movement has been repeated several times, this excessive tonus subsides, and the movement is performed in the normal way. A period of rest, however, is quickly followed by a return of the difficulty. The disturbance is usually most conspicuous in the muscles of the arms and legs.

The peculiarity of motion occurs only in voluntary movements. Muscular contractions are slower than normal, and the muscles involved remain more or less contracted for some seconds. The contraction is so powerful that the antagonistic muscles cannot overcome it. If a voluntary movement is repeated several times, the patient begins to perform each movement before the preceding contraction has been completely relaxed, and his difficulty as regards the stiffness gradually diminishes in each movement.

White[4] sums up the difficulty quite well: Flexion of the fingers usually illustrates the peculiarity of the disease; it is obvious that the flexor muscles contract more slowly than normally; they appear to remain completely contracted for from 1 to 3 seconds, and then are not at once completely relaxed, for if the patient is told to open the hand as quickly as possible, it is often between 7 and 10 seconds before the extensors completely overcome the flexors. If flexion be repeated as rapidly as possible, the second contraction obviously occurs more rapidly than the first, the third more rapidly than the second, and after about a half dozen contractions, the action appears quite normal. The difficulty is the same whichever muscles are affected, and different patients find different movements particularly difficult.

Such a defect has never been recorded in the acts of swallowing,

respiration, micturition, defecation, or parturition. With these exceptions, the stiffness may be observed in any movement executed by voluntary muscles. No reports of any sensory disturbance in this disease have been found, and the optic disks, when examined, have appeared healthy.

The characteristic alterations found in the electrical reactions are as follows:

1. Mechanical stimuli to motor nerves: no increase in irritability.
2. Faradic current to motor nerves: quantitatively normal; with strong current, the contraction produced on closing the circuit lasts much longer than normally.
3. Galvanic current to motor nerves: same as with faradic current.
4. Mechanical stimuli to muscles: contractions induced more easily than in health; contractions may last from 5 to 30 seconds.
5. Faradic current to muscles: if strong current, contraction lasts from 5 to 30 seconds.
6. Galvanic current to muscle: K.C.C. and A.C.C. are equally easy to obtain (in health, K.C.C. is much more readily elicited than A.C.C.).

In general it may be said that the contraction induced in muscles of individuals with Thomsen's disease lasts longer than in normal persons even when weak currents are used, and that with strong currents, the contraction lasts some seconds and relaxes quite slowly. The same patient does not usually exhibit all of the features of the electrical reactions usually classed as characteristic of this disorder.

The usual pathologic picture is marked hypertrophy of the affected muscles, which are firmer than is normal tissue when in action. Microscopically, the muscle fibers are usually considerably hypertrophied, some being 2 to 4 times the normal size; it is reported that on cross section the bundles of fibrillæ, instead of having the normal polygonal form, are much rounder than normal, some being almost circular. Longitudinal sections may reveal an increase in the number of muscle nuclei.

The disorder is essentially chronic, usually progressively increasing up to puberty, or even later. Relapses and remissions are not uncommon. Instances of complete recovery have not been reported, although the disease does not of itself lead to death.

Case Report. The patient (No. 33-14701), a white male, aged 19, was admitted to Dr. Stengel's ward in this hospital, complaining of stiffness of numerous joints and muscles. As long as he can remember the patient has had some difficulty in the initiation of muscular movements of all parts of the body. This was not especially troublesome, however, until the age of 15, but during the past 4 years has become progressively worse.

Movements cannot be initiated as rapidly as in the normal individual but must be begun slowly, as though there were a partial inhibition of action when first undertaken. After a particular movement has been performed several times, the involved muscles seem to respond better and soon the

motion can be performed as rapidly as normally. Following a rest period of several minutes, initiation of movement is again slow; for example, the patient cannot arise from a chair and immediately begin to run. He must start by walking slowly, then walk fast, then trot, and finally can run as fast as his classmates. He described nothing abnormal concerning his sensation of motion. The only other symptom of which the patient is aware is excessive hidrosis, which has been present since childhood. No loss of weight has been noted.

Both the father and a younger sister are troubled with a similar condition, but to a lesser degree. The sister has in addition a tendency to soreness and pain in the muscles and joints. The mother and brother of the patient and other relatives, so far as is known, are free from any similar complaint, nor is there a reliable history of the condition in earlier generations.

His past medical history is negative. He is a senior in high school, and engages in athletics. However, during the rest periods in any athletic contest, he must be in motion continuously to avoid developing stiffness in the various muscles.

Upon physical examination he was found to be a quite heavily muscled lad weighing 167 pounds stripped, 68 inches in height without shoes, intelligent and coöperative. Upon exertion of the slightest degree (such as slow walking), his face was bathed with droplets of perspiration and the skin became very pink. Examination of the heart, lungs and abdomen was essentially negative. Peripheral reflexes (biceps, triceps, patellar and Achilles) were normal.

Initiation of movements was definitely retarded and all motions were begun quite slowly. After repetition these gradually became faster. The disturbance was most marked in the extremities. After rising from a chair, the patient could not begin to take a forward step for several seconds and then advanced very slowly and "stiff-leggedly." After a half dozen steps he could walk normally. Difficulty in initiating motion was most marked when the antagonistic muscles had been contracted strongly. For example, voluntary motion at the elbow was quite free if the range of motion was not great and if there was an effort to keep the limb relaxed. However, if the patient strongly flexed his forearm on the upper arm he could subsequently extend it only slowly and with effort. After grasping the examiner's hand tightly, the patient could open his hand only with great difficulty; however, after repeating this several times, he performed this motion easily and quickly.

Among the routine laboratory studies, the following were normal: complete blood count, urinalyses, blood Wassermann with all antigens, blood urea nitrogen, blood sugar, serum calcium, phosphorus, and protein and the electrocardiogram. His basal metabolic rate was −14%. The therapeutic effect of 25 gm. of glycin continued daily for 7 days was tried but no beneficial results were noted, and 24-hour specimens of urine showed no creatin during the period of administration. This occasioned no surprise in view of the dissimilarity between this condition and the forms of myasthenia and muscular dystrophy in which benefit has been reported from glycin therapy.

A biopsy, taken from the left gastrocnemius muscle, was examined by Dr. E. B. Krumbhaar and compared with a similar specimen from a supposedly normal individual of the same age and sex. His report is as follows: "As compared with a slide of a normal gastrocnemius (boy of 22, PGH. Aut. 24731, October, 1934), the loss of compactness of each fiber is striking. The cross striations are very faint, the longitudinal fibrilli very prominent, often shredded out, with no visible sarcolemma, so that boundaries of the muscle fiber occasionally cannot be determined. The size of the longitudinal

cut fibers is somewhat larger than normal—an average measurement of 20 of each gives a diameter of 68 μ, *vs.* 52 μ of the normal. The difference in size is more marked in the cross-section (Figs. 1 and 2) which also shows the 'shredding' effect, the average area of 20 fibers being more than twice that of 20 normal fibers (diam. 76 *vs.* 54 μ). A minor factor in this increase is the increased space between the fibrils. The muscle nuclei did not seem to be increased. Schiefferdecker's (Deut. Ztschr. f. Nervenheilk. **25**, 1, 1903) droplets or granules were not seen. The section is certainly not normal muscle tissue."

Electrical reactions, performed by Dr. M. J. Cooper, revealed in the right anterior thigh muscles an increased muscular irritability to faradic current and some increased irritability to galvanic stimulation. The contraction of the muscle was strong but its relaxation was distinctly slow and gradual. A.C.C. was approximately equal to K.C.C. In the left anterior thigh muscles, similar but less distinct reactions were obtained; in the calf and peroneal muscles on each side there was increased faradic irritability, A.C.C. being approximately equal to K.C.C., but no distinct sluggishness of relaxation after electrical stimulation of these muscles was manifest. The excitability of the nerve trunks of the lower limbs was approximately normal. The muscles of the upper limbs showed very little abnormality in the response to electrical stimulation, except the posterior part of the right deltoid, which exhibited a slowness of relaxation after tetanic contraction to faradic stimulation, and the intrinsic muscles of the hands, which showed a slight reduction of electrical excitability, and some sluggishness both of contraction and relaxation.

Various muscles (left triceps and biceps, and right gastrocnemius) were tested with needle electrodes by Dr. G. Gammon. It was found that at the beginning of voluntary movements, especially if forced, a spasm resulted which could not be voluntarily relaxed. This contraction of the muscle was accompanied by normal action currents, and the failure to relax was not due to any weakness of the opposing muscles which were put into use to straighten out the limb. The action currents outlasted the patient's knowledge of contraction. Repetition of the movement rapidly resulted in failure of appearance of the spasm. No action currents were present when the muscle was not in spasm. The effective spasm was present even though the opposing muscle was not thrown into play. No studies were made on obtaining the phenomenon by reflex action. All of the muscles studied showed this same effect. These action potentials are to be interpreted as arising from the contracting muscle and not from its nerve supply. One cannot definitely determine from these whether the origin of the spasm is nervous or muscular.

NOTE.—Since this article was written, the patient was placed on ephedrin sulphate, gr. $\frac{3}{8}$ t. i. d. by mouth, with marked subjective improvement.

Discussion. This case seems worthy of report because of the paucity in the American literature of accounts of families with this disease, and because of the unfamiliarity of many internists with the clinical picture. In fact, this patient had been treated elsewhere over a period of years with a diagnosis of arthritis because of his chief complaint of stiffness of the muscles and joints. The outstanding feature of the disease is the stiffness of voluntary movement on effort. The myotonia may become much more marked under emotional stress or exposure to cold. Warmth is said to decrease the tone.

Various hypotheses have been advanced concerning the nature of

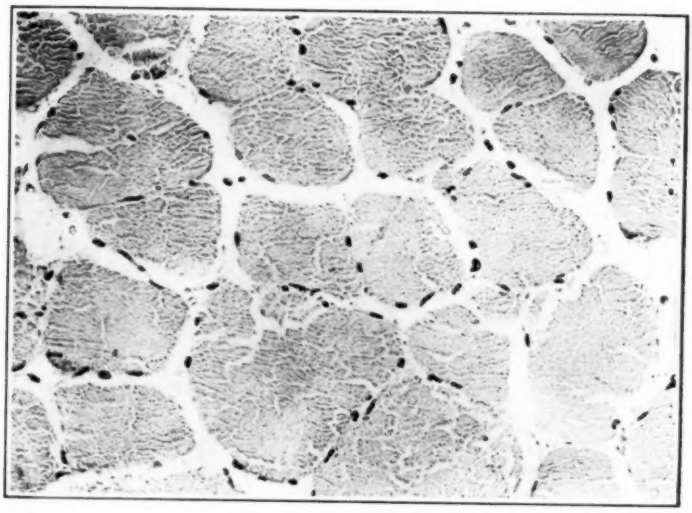

FIG. 1

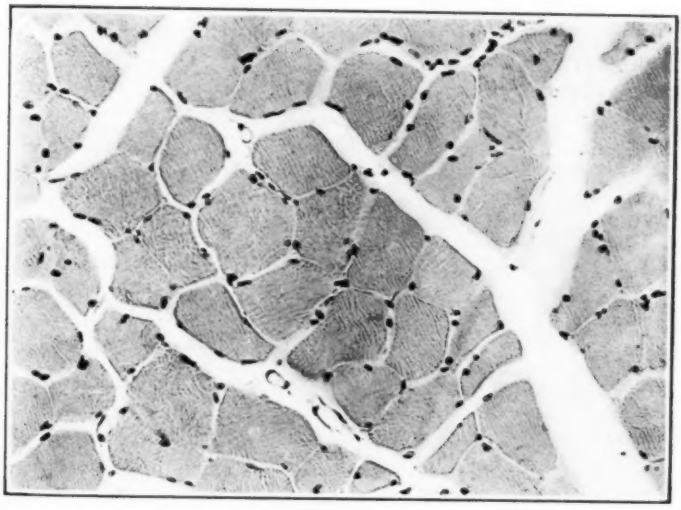

FIG. 2

the disorder; these include a myopathy, disease of the sympathetic nervous system, endocrine dysfunction, and a parasympathetic disturbance of muscle tone in some way related to endocrinopathy (especially the thyroid or parathyroid glands).[6] It has been reported[7] that the individual muscle fibers possess an excessive proportion of undifferentiated sarcoplasm, which latter in contrast to the fibrillar element of muscular tissue, is said to contract and relax with a slow muscle wave, thus accounting for the sluggish contraction and relaxation seen in this condition.

Conditions sometimes confused with Thomsen's disease include paramyotonia congenita, amyotonia congenita, myotonia atrophica, and progressive muscular dystrophy. The tonic spasms occurring in the voluntary muscles in paramyotonia congenita (Eulenberg's disease) are induced by exposure to cold, and not by exertion. They are most commonly found in the face, and may persist for 10 to 15 minutes. Amyotonia congenita (myatonia congenita, Oppenheim's disease) is characterized by extreme flaccidity of muscles with diminished electrical excitability to faradic and galvanic current. The extremities can often be placed in all sorts of abnormal positions of hyperflexion or hyperextension without pain or discomfort. Myotonia atrophica is probably closely related to Thomsen's disease, occurring usually after the twentieth year, and in which general wasting is a conspicuous feature. Cataract is frequently found in families of the patients.[5] Pathologically the muscle fibers appear quite small, but contain all the markings of normal muscle tissue.[8]

Under the heading of progressive muscular dystrophy (myopathies) is considered a number of muscular disorders probably not of spinal origin. They differ from the true muscular atrophies according to Spiller[9] in that they are hereditary or familial, they begin early in life, there is usually involvement of the trunk, pelvic or shoulder girdle muscles before the distal portions of the extremities, no true reactions of degeneration are present, and there are no fibrillary tremors. Of the more important subdivisions of the myopathies, three may be mentioned: the muscular pseudohypertrophy which affects chiefly the calves, and is accompanied by atrophy of the muscles of the thighs, back, shoulder, scapula, and of the calves themselves at a later date. Second, there may be noted the juvenile form (Erb's type) in which the hypertrophy is noted especially in the muscles of the shoulder and pelvic girdles. Third, there is the Landouzy-Dejerine or facio-scapulo-humeral form in which no hypertrophy is usually seen, but in which atrophy begins in the face and shoulder girdle muscles. In the myopathies, Grinker states that the essential pathologic process is a large degree of swelling of the muscle fibers, with breaking up of the striations and the appearance of large fatty vacuoles in the sarcoplasm.

Summary. 1. A case of congenital myotonia (Thomsen's disease) is presented with a short résumé of the important features of this disorder.

2. Biopsy section of the affected muscle is presented.

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BOOK REVIEWS AND NOTICES

Diseases of the Mouth and Their Treatment. A Text-book for Practitioners and Students of Medicine and Dentistry. By Hermann Prinz, A.M., D.D.S., M.D., D.Sc. Dr. Med. Dent., Professor of Materia Medica and Therapeutics, The Thomas W. Evans Museum and Dental Institute, University of Pennsylvania, and Sigmund S. Greenbaum, B.S., M.D., Associate Professor of Dermatology and Syphilology in the Graduate School of Medicine of the University of Pennsylvania. Pp. 602; 287 illustrations and 11 colored plates. Philadelphia: Lea & Febiger, 1935. Price, $9.00.

There is everything to praise and little to criticize in this book. It is well bound, printed on glossy paper and the illustrations are abundant and excellent. The treatise begins with anatomy and physiology, continuing with methods of examination of the oral cavity and followed by generalities as to symptomatology of disease of the mucous membranes, teeth and gums as well as oral hygiene and dental prophylaxis. After these preliminaries the special disease entities of the mucous membranes as well as of teeth and related areas of the skin of the face are dealt with individually and systematically. Particular emphasis is placed on pathology. It is difficult to understand how any dentist or physician, particularly the dermatologist, could do without this volume. F. W.

To Remind: A Biological Essay. (The Abraham Flexner Lectures, Series No. 2.) By Sir William Bate Hardy, M.A. (Cantab.), F.R.S., Hon. D.Sc. (Oxon.), Hon. LL.D. (Aberdeen, Edinburgh, Birmingham), Fellow of Gonville and Caius College; Director of Food Investigation, Department of Science, Industrial Research, etc. Pp. 45. Baltimore: The Williams & Wilkins Company, 1934, for Vanderbilt University. Price, $1.00.

The second series of the Abraham Flexner Lectures in the School of Medicine of Vanderbilt University was delivered in February and March, 1931, by the late Sir William Bate Hardy. At the time of his death only the two lectures here published had been prepared for publication: a charming philosophic speculation on the riddle of life as exemplified in the fundamental living substance: protoplasm, and the asymmetry of molecular structure in living matter. R. K.

The Principles of Therapeutics. (The Abraham Flexner Lectures, Series No. 3.) By Francis Richard Fraser, M.A. (Cantab.), M.D. (Edin.), F.R.C.P. (Lond.), Professor of Medicine in the University of London. Pp. 135. Baltimore: The Williams & Wilkins Company, 1934, for Vanderbilt University. Price, $2.00.

The third series of the Abraham Flexner Lectures, delivered in 1933, in the School of Medicine of Vanderbilt University, in which Professor Fraser discusses for his student hearers the principles which underlie the rational treatment of disease, using as his texts: historic consideration of the development of therapeutics; the treatment of the causes of disease; treatment based on symptoms; the care of the patient. This little book should be read by all senior students. R. K.

POLIOMYELITIS. A Handbook for Physicians and Medical Students. By JOHN F. LANDON, M.D., Attending Physician, Willard Parker Hospital; Special Consultant in Pediatrics, Woman's Hospital, New York, etc., and LAWRENCE W. SMITH, M.D., Pathologist, Willard Parker Hospital, etc. With a Section on the orthopedic after-care of the disease by GARRY DEN. HOUGH, JR., M.D., F.A.C.S., F.A.A.O.S., Attending Orthopedic Surgeon, Shriner's Hospital for Crippled Children, Springfield, Mass. Pp. 275; 18 illustrations. New York: The Macmillan Company, 1934. Price, $3.00.

"THE 1931 New York City epidemic of poliomyelitis afforded the authors an unusual opportunity to observe an exceptionally large amount of clinical and pathological material . . . . Approximately 1000 cases were admitted to the Willard Parker Hospital during that summer and 81 autopsies were performed . . . . These and some 1400 additional cases occurring in the other communicable disease hospitals of the Department of Hospitals have been exhaustively studied . . . . It is the aim and hope of the authors to present in this short volume a well rounded and compact exposition of the disease, ... including an unbiased evaluation of serum therapy, the use of the respirator, the after care, etc., which will enable the general practitioner and the student to obtain a practical working knowledge of the disease." The authors have achieved their aim: the book is a well-balanced, concise, accurate presentation of the subject. Also worthy of mention are the appendices, describing the nursing care of poliomyelitis, the aseptic technique used in the Willard Parker Hospital, and the New York City Health Department regulations concerning this disease. R. K.

FOOD AND HEALTH. By HENRY C. SHERMAN, Mitchill Professor of Chemistry, Columbia University. Pp. 296. New York: The Macmillan Company, 1934. Price, $2.50.

THE best presentation of practical dietetics for the well, who would remain so, that has come to the knowledge of the Reviewer. "This book is not written by a physician nor for those who are ill; it is for those who wish to maintain and enhance their health, and the health of any others for whose food selection they may be responsible." The writer's distinguished achievements in the field of the chemistry and physiology of nutrition eminently qualify him to present the subject. This he has done in a clear, lucid manner, and from a sound conservative viewpoint. Written for the intelligent layman, the book always preserves a scholarly and scientific tone, not falling into the "journalese" style of so many medical books for lay consumption. It is warmly recommended to all readers, lay and medical, who wish an accurate, concise and practical exposition of our present-day knowledge of food and its relation to health. R. K.

THE NEW-BORN BABY. A Manual for the Use of Midwives and Maternity Nurses. By ERIC PRITCHARD, M.A., M.D. (OXON.), F.R.C.P. (LOND.), Medical Director, Infants Hospital, London; Pediatrician to Queen Charlotte's Maternity Hospital, etc. Pp. 272; 9 illustrations. London: Henry Kimpton, 1934. Price, 4/6.

THIS little book is simply and plainly written and contains adequate information for nurses specially trained in obstetrics or for midwives. All books of this type probably err on the side of presenting too much provender for partakers of the fare. One notes slight differences of opinion as to the use of certain materials and which may be common practice in England,

For instance, the author feels that any artificial food containing cow's milk should be peptonized before being offered to a new-born infant. In the United States we are apt to feel that boiling, or acidification, or both, modify the milk best.

The author unfortunately introduces a controversial matter that might well be omitted. He feels that pyloric stenosis is acquired and not congenital—that it is the end result of habitual vomiting. There are few who will agree with him. S. T., Jr.

The Vitamin B Requirement of Man. By George R. Cowgill, Ph.D., Associate Professor of Physiological Chemistry in Yale University. Pp. 261; 8 illustrations, 81 tables and 8 charts. New Haven: Yale University Press for The Institute of Human Relations, 1934. Price, $4.00.

From data accumulated over a considerable period of research upon several species of animals (rat, pigeon, mouse and dog) and upon individuals of different size in the same species, Cowgill has derived a mathematical formula applicable to the vitamin B requirements of each species, the important variables in the calculation being weight, metabolism (calories) and maximum (or adult) weight. This formula he finds can be applied satisfactorily to the requirement of the human species.

The monograph reviews in detail the experimental work and the steps by which the formula was derived and confirmed. It includes also tables of foodstuffs in terms of their unit content of vitamin B and analysis of the vitamin/calorie ratio of diets known to have produced or to have failed to produce beri beri, as reported in the literature of various epidemics of beri beri. The predicted result of such diets in terms of their adequacy in vitamin B is compared with the actual result (*i. e.*, the presence or absence of beri beri).

The book is written in terms that any well-informed reader can understand. A considerable bibliography is appended. E. W.

American Medicine. By Henry E. Sigerist, The William H. Welch Professor of the History of Medicine, The Johns Hopkins University. Translated by Hildegard Nagel. Pp. 316; illustrated. New York: W. W. Norton & Co., Inc., 1934. Price, $4.00.

From the time of de Tocqueville just a century ago, some of the best evaluations of America have come from foreigners—not that we must any longer call Sigerist a foreigner, but such he was when this book was conceived during a tour of the country in 1931 and 1932. An account of the development of American medicine, this book opens with brief descriptions of Indian medicine, colonial times and non-medical United States, by way of background. The chapter on Pioneers, the longest in the book, carries us from John Morgan to Osler and the founding of the Johns Hopkins Medical School. In 56 short pages it gives in the author's graceful, sparkling style a fine bird's-eye view of a full century—the discovery of anesthesia, for instance, being presented from an obviously adequate knowledge of the subject. The chapters on Medical Education and Medical Science paint in swift bold strokes the lights and shadows of these developments, seen—as is perhaps natural—through Baltimore-tinted glasses. In the chapters on Physician and Patient, on Hospitals and Nursing, and on Preventive Medicine some of the social aspects of medicine in this country are touched upon in a way that is particularly illuminating, coming as it does at this time and from an accomplished historian and keen cosmopolitan observer, fresh on our scene. The extensive bibliography and indices testify to the large amount of ground covered; for an appreciation of the narrative charm, the book must be consulted at first hand. E. K.

STAMMERING AND ALLIED DISORDERS. By C. S. BLUEMEL, M.A., M.D., F.A.C.P., M.R.C.S. (ENG.). Pp. 182. New York: The Macmillan Company, 1935. Price, $2.00.

CONSIDERING speech as a conditioned reflex, the writer theorizes that stammering results from faulty inhibition which "checks, quenches, blocks or impedes" vocalization. It is suggested that the male preponderance—four to one—may be due to a less stable conditioned reflex.

Primarily, the disorder shows partial inhibition; later, the child may become conditioned to various speech situations. If the stammering has begun abruptly, it may be aborted through rest and sedation. Failing in this, fatigue and excitement should be avoided and the more technical procedure, including "transquillization," "reënforcement" and "unconditioning" may be required. The text is lucid, the references abundant and the index informative. N. Y.

THE TECHNIQUE OF POSTMORTEM EXAMINATION. As Practiced in the Pathological Institute of McGill University at the Royal Victoria Hospital, Montreal. Compiled by D. R. COMAN, M.D., C.M., Assistant to the Instructor and Demonstrator in Pathological Anatomy. Pp. 47; 12 illustrations. Montreal: Renouf Publishing Company, 1934. Price, $1.40.

A SMALL book on this subject, accurate and with adequate directions for performing necropsies, has long been needed to put into the hands of the pathological aspirant. Except for the translation of Virchow's booklet, "Postmortem Examinations," we know of none such in English. The present book, conveniently arranged with interleaved blank sheets, details the procedure used at the McGill Pathological Institute. In general, the technique is much like Virchow's. A few special procedures are added, together with a table of normal weights and a method for frozen section technique. With the increasing recognition of the value of necropsies in medical schools and hospitals, it is not too much to expect that every graduate of a first class medical school should have learned the technique and occasionally perform a necropsy—this booklet will show him how.

E. K.

DIE NEUROLOGIE DES 1.–7. JAHRHUNDERTS N. CHR. EINE HISTORISCH-NEUROLOGISCHE STUDIE. Sammlung Psychiatrischer und Neurologischer Einzeldarstellungen. Band VI. By DR. WALTER CREUTZ, Oberarzt an der Prov.-Heil- und Pflegeanstalt, Düsseldorf-Grafenberg und der psychiatrischen Klinik der medizinischen Akademie, Düsseldorf. Pp. 106. Leipzig: Georg Thieme, 1934. Price, M. 7.80.

NEUROLOGY has so recently become an independent specialty in medicine that its age-old history has not acquired much of a separate footing. This book is a praiseworthy attempt to sketch of the picture of classical neurologic knowledge during the first seven centuries of the Christian era, and of the seeds carried over through Arabian Medicine and the School of Salerno for the developments of the Renaissance and modern times. The first half of the book considers, with liberal excerpts, the neurologic contributions of Celsus, Soranus (Caelius Aurelianus), Galen, Aretaeus, Cassius, Oribasius, Aetius, Alexander of Tralles and Paul of Aegina. The latter half of the book assembles the neurologic knowledge of the period under the heading of Anatomy and Physiology, Paralysis, "Canina convulsio" (tic, facial palsy?), sciatica, lumbago, apoplexy, "Diminutio cerebri" (cerebral thrombosis?), epilepsy. E. K.

NEW BOOKS.

Blood Groups and Blood Transfusion. By ALEXANDER S. WIENER, A.B., M.D. Pp. 220; 41 illustrations and 72 tables. Springfield, Ill.: Charles C Thomas, 1935. Price, $4.00.

Martini's Principles and Practice of Physical Diagnosis. Edited by ROBERT F. LOEB, M.D., Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University, and Presbyterian Hospital, New York. From the authorized translation by GEORGE J. FARBER, M.D. Pp. 213; 30 illustrations. Philadelphia: J. B. Lippincott Company, 1935. Price, $2.00.

Prassi Medico-Forense. By PROF. DOTT. FRANCESCO BALLOTTA, Ainto e Docente nell'Institute di Medicina Legale della R. Università di Bologna. Pp. 167; 21 illustrations, some in colors. Bologna: Nicola Zanichelli, Editore, 1935. (Price not given.)

The Cyclopedia of Medicine. Index to Volumes 1 to 12. GEORGE MORRIS PIERSOL, B.S., M.D., Editor-in-Chief, and EDWARD L. BORTZ, A.B., M.D., Assistant Editor. Chief Associate Editors: W. WAYNE BABCOCK, A.M., M.D., CONRAD BERENS, M.D., P. BROOKE BLAND, M.D., FRANCIS I. LEDERER, B.S., M.D., and A. GRAEME MITCHELL, M.D. Pp. 415. Philadelphia: F. A. Davis Company, 1934. Price, $120.00 for set.

The Dangerous Age in Men. A Treatise on the Prostate Gland. By CHESTER T. STONE, M.D., Clinical Assistant Surgeon, Urologic Division, Bellevue Hospital, New York City; Urologist, Bergen County Hospital, Oradell, N. J.; Consultant Urologist, Rome State School, Rome, N. Y. Pp. 105. New York: The Macmillan Company, 1935. Price, $1.75.

The Patient and the Weather. Vol. II. Autonomic Dysintegration. By WILLIAM F. PETERSEN. With the assistance of MARGERET E. MILLIKEN, S.M. Pp. 530, lithographed; 249 illustrations. Ann Arbor, Mich.: Edward Brothers, Inc., 1934. Price, $6.50.

International Clinics, Vol. I, Forty-fifth Series, 1935. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, Md., with 14 collaborators. Pp. 310; illustrated. Philadelphia: J. B. Lippincott Company, 1935.

Among the authors of the 9 medical and 5 surgical papers appear such well-known names as Wilder, Stroud, Haden, Musser, Grier Miller, C. C. Norris and Hans Hanke of Freiburg. The Recent Progress articles are by Cantarow on Cholesterol Metabolism, and by Goodwin and Balfour on Surgery.

The Nervous Patient. A Frontier of Internal Medicine. By CHARLES PHILLIPS EMERSON, M.D., Research Professor of Medicine, Indiana University, Indianapolis. Pp. 453. Philadelphia: J. B. Lippincott Company, 1935. Price, $4.00.

A Manual of Biochemistry. By J. F. MCCLENDON, Professor of Physiological Chemistry, University of Minnesta Medical School. Pp. 381; 58 illustrations. New York: John Wiley & Sons, Inc., 1934. Price, $5.00.

NEW EDITIONS.

What You Should Know About Heart Disease. By HAROLD E. B. PARDEE, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical School; Associate Attending Physician, New York Hospital, etc. Pp. 127; 4 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, $1.50.

"Heart disease is now recognized as an important public health problem, as is evidenced by the growth of the numerous Heart Associations . . . . The patient must understand his own condition if he is to coöperate in its cure and avoid the unpleasant results of the disease . . . . The first purpose of this book is to help the patient to follow his physician's directions intelligently." (Publisher's note.)

Physical Diagnosis. By WARREN P. ELMER, B.S., M.D., Associate Professor of Clinical Medicine, Washington University School of Medicine; Assistant Physician to Barnes Hospital, etc.; and W. D. ROSE, M.D., late Associate Professor of Medicine in the University of Arkansas. Pp. 919; 342 illustrations. Seventh edition. St. Louis: The C. V. Mosby Company, 1935. Price, $8.00.

"The general form of the book has not been altered. New matter, especially on aortic murmurs, silicosis and diagnostic methods, has been added in order to make the work more complete and up-to-date. The sections on electrocardiography have been completely revised. Several new illustrations have been added." (From Author's Preface.)

Diseases of the Skin. By RICHARD L. SUTTON, M.D., Sc.D., LL.D., F.R.S. (EDIN.), Professor of Dermatology, University of Kansas, School of Medicine, and RICHARD L. SUTTON, JR., A.M., M.D., L.P.C.P. (EDIN.), Assistant in Dermatology, University of Kansas, School of Medicine. Pp. 1433; 1310 illustrations and 11 colored plates. Ninth edition, revised and enlarged. St. Louis: The C. V. Mosby Company, 1935. Price, $12.50.

Methods of Treatment. By LOGAN CLENDENING, M.D., Clinical Professor of Medicine, Medical Department of the University of Kansas; Attending Physician, Kansas City General Hospital, etc. With chapters on special subjects by H. C. ANDERSSON, M.D., URSULLA BRUNNER, R.N., J. B. COWHERD, M.D., PAUL GEMPEL, M.D., H. P. KUHN, M.D., CARL O. RICKTER, M.G., F. C. NEFF, M.D., E. H. SKINNER, M.D., E. P. DEWEESE, M.D., and O. R. WITHERS, M.D. Pp. 879; 102 illustrations, Fifth edition. St. Louis: The C. V. Mosby Company, 1935. Price, $10.00.

Useful Drugs. A List of Drugs Selected to Supply the Demand for a Less Extensive Materia Medica, with a Brief Discussion of Their Actions, Uses and Dosage. Edited by ROBERT A. HATCHER, PH.M., Sc.D., M.D., and CARY EGGLESTON, M.D. Prepared under the direction and supervision of the Council on Pharmacy and Chemistry of the American Medical Association. Pp. 203. Ninth edition. Chicago: American Medical Association, 1934. Price, 60 cents.

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Diseases of the Rectum and Colon and Their Surgical Treatment. By J. P. LOCKHART-MUMMERY, F.R.C.S. (ENG.), M.A., M.B., B.C. (CANTAB.), Senior Surgeon to St. Mark's Hospital for Cancer, Fistula and Other Diseases of the Rectum, etc. Pp. 605; 250 illustrations. Second edition. Baltimore: William Wood & Co., 1934. Price, $10.00.

PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF

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THE TREATMENT OF HEART FAILURE AND ANGINA PECTORIS BY TOTAL THYROIDECTOMY.

THIS radical therapeutic procedure was first suggested by Blumgart, Levine and Berlin[1] less than 2 years ago. The genesis of the idea dates back to Levine's[2] observation of a single patient[3] upon whom a subtotal thyroidectomy had been performed in 1927 for the relief of chronic, intractable heart failure believed possibly to have been associated with latent or "masked" hyperthyroidism.[4] Despite the fact that the thyroid gland of this patient was found to be normal both grossly and microscopically, she recovered promptly from her congestive heart failure and remained well for 3 years. Thereafter mild congestive heart failure began to reappear and the patient succumbed to it $4\frac{1}{2}$ years following the operation. The remarkable results obtained in this patient led to the trial of almost complete subtotal thyroidectomy as a means of relieving either intractable congestive heart failure or chronic, resistant angina pectoris in a small additional group of patients without clinical hyperthyroidism.

Study of these additional patients showed that while such subtotal thyroidectomy would cause a marked fall in the level of the basal metabolism, this reached its limit in a few weeks, after which it would return to normal or to the pre-operative level. Improvement in the cardiac symptoms was observed to be limited almost wholly to the brief period of lowered metabolic rate, the congestive failure or angina then promptly reappearing. These observations, when considered in conjunction with previous studies on the relation of the velocity of blood flow to the level of the basal metabolic rate,[1] led Blumgart to suggest the complete removal of the entire normal thyroid gland.

Accordingly, on December 15, 1932, the first operation for the complete therapeutic ablation of a normal thyroid gland was performed by Berlin[1] on a patient suffering from chronic rheumatic heart disease, mitral stenosis and insufficiency, auricular fibrillation, the anginal syndrome and chronic intractable congestive heart failure. The immediate results were dramatic. All signs and symptoms of both the congestive heart failure and the angina disappeared during convalescence from the operation, and less than 4 months after operation the patient was working 8 hours daily without cardiac symptoms. On the basis of the striking benefits secured in this first patient more than a hundred patients have already been subjected to the procedure.[6,7]

Theoretical Bases Underlying Total Thyroidectomy. *Its Rationale.* With the development of more delicate and more accurate methods of investigation Blumgart[6,8] and his associates embarked upon an extensive series of studies of variations in the rate of blood flow in man in health and disease. They showed that in normal persons the rate of blood flow was directly determined by the metabolic demands of the body. These, in turn, were measured by the metabolic rate. Whenever the level of basal metabolism was elevated the velocity of blood flow was found correspondingly accelerated, if the circulatory system were normal. Uncomplicated hyperthyroidism was always accompanied by an increased rate of blood flow. Conversely, uncomplicated myxedema showed a diminished rate of blood flow. In each of these conditions the rise or fall in the velocity of blood flow was more or less directly proportional to the level of the metabolism.

The presence of heart disease was observed not to upset this established relationship between metabolic rate and velocity of blood flow so long as the heart disease was fully compensated. When congestive failure was present this relationship no longer existed and the rate of blood flow was retarded even when the basal metabolism was normal. In patients showing various degrees of congestive failure the retardation in the velocity of blood flow was more or less proportional to the severity of the cardiac failure. It was further observed that the rate of blood flow in myxedema was often as slow as that recorded in cardiac patients who were decompensated, yet the myxedematous patients were without evidences of circulatory failure. This observation led Blumgart to the deduction that, "The adequacy of a given speed of blood flow can be decided only in relation to the metabolic needs of the tissues."[9]

These and other related observations and considerations led Blumgart[5] and his collaborators to make the following statement: "The thought, therefore, arose that if the normal metabolic rate of the patient with congestive failure were reduced, his blood supply, while not necessarily altered, might nevertheless be sufficient for the lowered needs of his body. In terms of the law of supply and demand, the supply of blood in such a patient with congestive failure would not be increased, but the metabolic demands of his body would be decreased to a level in conformity with his blood supply."

The modern conception of angina pectoris holds that the pain is due to the inadequacy of the coronary circulation in proportion to the work of the heart, that is, to the rate of cardiac metabolism. Total thyroidectomy, while not increasing coronary blood flow, may be expected through reduction in the metabolic rate of the heart muscle, to restore the bal-

ance between these two factors and thereby prevent the development of the attacks.*

Support of the foregoing theory of the close relationships between the metabolic demands of the tissues and the production of heart failure of either the congestive or the anginal type is found in the clinical observations which have previously been recorded in patients with hyperthyroidism. Even as long ago as 1902, Kocher[10] observed and recorded the relief of congestive cardiac failure following subtotal thyroidectomy. This has, of course, been abundantly confirmed by others, especially by the extensive studies of Hamilton[11] and by the observation of the effects upon cardiac failure produced by diminishing basal metabolism in hyperthyroidism by the administration of iodin.[12] The reports by Morris[13] of the beneficial effects of subtotal thyroidectomy in a group of thyrotoxic patients having normal or subnormal metabolic rates are also of significant bearing. In contrast to them there stand, however, numerous reports recording the failure to influence cardiac and other circulatory symptoms by subtotal thyroidectomy performed on patients who were free from demonstrable thyrotoxicosis.

Approaching the problem from the opposite angle, there is a number of observations cited by Blumgart and his associates[5] in which the elevation of basal metabolism by the administration of thyroid to patients with myxedema was observed to produce attacks of angina pectoris and other symptoms of circulatory inefficiency.

Selection of Cases for Further Study and Methods of Investigation. In order to put this radical therapeutic procedure to a thorough test and at the same time to avoid unnecessary risks cases were chosen with much care. Only such patients were selected whose prognoses for useful life were very doubtful or definitely poor. Yet no patient was selected who did not seem to be a fair surgical risk, or in whom the risks from the operation could not be made fair by pre-operative treatment. All patients with congestive failure had been under observation and treatment for considerable periods of time and all were such as could not be kept free from symptoms of failure when out of bed. Most, however, could be comfortable and without symptoms under treatment when bedfast. In every such patient any benefit which might follow total thyroidectomy could justly be ascribed to the operation. Similar rigid criteria were applied to the selection of patients with angina. Each patient was generally studied independently by several physicians before final decision. Blumgart says,[5] "No better gauge of the predicament of most of these patients could be found than their pathetic desire to hazard any of the dangers involved in order to secure possible benefit after having suffered for many years and after having observed their condition become progressively worse in spite of medical treatment."

A wide variety of types of cardiovascular disease was included in the group selected. There were cases with arteriosclerotic heart disease with angina, some with congestive failure, and some with hypertension

* [Note: It is probable that the mechanism of the production of angina pectoris is not always so simple as this and involves one or more of several additional factors not the least of which appears to be the state of the central nervous system. —Editor.]

and paroxysmal dyspnea. Failure due to chronic rheumatic heart disease was included, both with and without auricular fibrillation. There was also right ventricular failure with cor pulmonale. Patients were rejected if they showed active rheumatic infection, recent vascular accidents, or were in the active stages of acute cardiac infarction from coronary thrombosis. Syphilitic cardiovascular disease was also rejected because of the known tendency of this form of failure to progress rapidly. All accepted patients were free from evidences of existing thyrotoxicosis, and none had a history of its previous existence. Postoperative study of the removed glands showed them to have been normal in every case but one. No physically immature patient was operated upon because of the risks of cretinism. Finally, no patient was accepted who could not give a clear and accurate account of his symptoms.

Every patient was subjected to detailed clinical investigation both before and after the operation. These studies were generally made independently by several observers, and often extended over many weeks prior to operation in order to minimize the operative risks by suitable treatment. This pre-operative clinical study also served as a basis for accurate comparison of the changes which followed operation. Many purely objective data were recorded routinely and as often as necessary both before and after the operation. These included determinations of the blood pressures, vital capacity, and body weight, all made under standardized conditions. Other data included teleoroentgenograms of the heart, electrocardiograms, photographs of the patient, frequent determinations of the basal metabolism, measurements of venous pressure, determinations of the arm to tongue circulation time as an index of the rate of blood flow, and studies of the patient's reaction to exercise as determined by the Master and Oppenheimer[14] test carried out under standardized conditions.[15] Finally in addition to routine blood chemical tests, studies were made on the level of the content of many constituents of the blood, especially phosphate, calcium and cholesterol.

The Operation. *Certain Precautions; Anesthesia.* The selection of the anesthetic which can be used in seriously ill patients with the smallest margin of risk is both difficult and of the utmost importance. At first gas and oxygen were employed, supplemented when necessary with small amounts of ether. However, among a comparatively small group of cases there were six deaths from postoperative bronchopneumonia for which the anesthetic was believed largely responsible. Avertin was abandoned after a stormy postoperative course in 1 case. Local anesthesia was then adopted at the suggestion of Mixter[16] with almost complete elimination of postoperative anesthetic mortality. The use of local infiltration anesthesia with procain was found to simplify the surgical technique by separating the tissue planes and rendering certain steps easier. All of the postanesthetic deaths occurred in cases with congestive failure; anginal cases have been shown to be better surgical risks. The infiltration carries with it the risk of transient paralysis of the recurrent laryngeal nerve. This can be avoided by not infiltrating along the tracheoesophageal sulcus or deeply into the gland.

Great caution must be observed not to damage the recurrent laryngeal nerve. The entire thyroid gland must be removed, and Berlin[17]

found in a series of 140 dissections that this nerve partially penetrated the gland in 10%. In 25% the nerve passed through the area of fixation of the gland to the trachea just below the anterolateral region of the cricoid bar at the level of the first and second tracheal rings—this is the so-called adherent zone. The dangers of laryngeal nerve paralysis can be avoided by remembering these two abnormal locations and by always identifying the nerves and preserving them intact by painstaking blunt dissection. Of the nerves dissected 65% were found to be safely placed in the sulcus between the trachea and esophagus where they were well protected against operative injury.

It was found possible further to insure against the dangers of recurrent nerve damage and paralysis by observing the simple precaution of careful laryngoscopic examination[18] before operation and again after the dissection of one lateral lobe of the gland had been completed. This required interruption of the operation for but a few minutes. If such examination showed paralysis of the homolateral vocal cord, the operation was then terminated. If the nerve were proved to be uninjured then the operation could be successfully completed as observations have shown that the paralysis of one vocal cord is not a source of danger to the patient. It was first thought, when the operation was performed under local anesthesia, that the voice test would be satisfactory in revealing a cord paralysis but this was proved not to be the case. By the observance of these precautions unilateral paralysis of the recurrent laryngeal nerve occurred in only 12 of 85 consecutive operations.[20,21] In 9 the paralysis was temporary and was followed by complete recovery. Two patients who showed unilateral nerve injury by direct laryngoscopy and in whom the operation was, therefore, terminated, recovered from their paralysis and the thyroidectomy was successfully completed by a second stage operation at a later date.

Inasmuch as every vestige of the thyroid gland must be removed to prevent regeneration and restoration of normal basal metabolism, it is necessary for the surgeon to remember that the pyramidal lobe is found in 35% of patients. This must be searched for and dissected out with great care from between the trachea and esophagus.

This review is not the place to discuss the details of surgical technique, and the reader is referred to Berlin's[19] original description as well as to the preceding papers.[16,17] Surgeons should not undertake this operation without the precautions of familiarizing themselves with the experiences of others and without at least a few practice operations upon the cadaver. While the necessity for painstaking dissection renders the operation rather time consuming, the fact that the thyroid gland is normal renders its removal not particularly hazardous *per se* if the patient has been adequately prepared. The 6 operative deaths previously mentioned were the only ones in a consecutive series of 75 patients, giving an operative mortality of 8%. With the modifications, some of which have just been presented, there have been no operative deaths in the last consecutive 30 cases.

Preservation of the Parathyroids. Owing to the necessity for the complete removal of the thyroid gland in this procedure, the danger of damage to the parathyroid glandules or their accidental removal is much greater than in the common operation of subtotal thyroidectomy. Dissections upon the cadaver were carried out by Berlin[20] in order to

be familiar with the various locations in which these bodies were to be found and in order better to recognize them in the course of operation. In 66% of a series of 60 patients, the parathyroids were found to lie just above the lower poles of the thyroid gland where they were in close relation to the end branch of the inferior thyroid artery; 22% lay on the posteromedial aspect of the thyroid close to the junction of the middle and upper third of the adjacent lobe. They were found to lie scattered in various locations in the remaining 12%. Berlin[19] describes the parathyroids as yellowish-brown, flattened oval bodies about the size of a split pea and having a finely granular surface, an appearance especially useful in helping to distinguish them from lobules of fat and from the brownish-red coarse fragments of accessory thyroid tissue. The number of parathyroids present is variable and it is often difficult to demonstrate more than 2 or 3 of them during operation. The inferior ones are observed to be placed more laterally and are often supplied by a long arterial twig, hence their recognition and preservation is seldom difficult.

Armed with much of this knowledge before beginning the surgical removal of the entire thyroid gland, Berlin was able to carry out the operation on 75 consecutive patients in only 14 of whom was there any subsequent evidence of parathyroid deficiency. In all of these 14, the deficiency was controlled either without medication or by the use of calcium alone for comparatively short periods of time. In only 2 instances has it been necessary to continue the administration of calcium and in these the mild symptoms of hypoparathyroidism were completely controlled. It seems evident from these facts that the symptoms observed in these 14 patients were due not to the accidental removal of the parathyroid glands but rather to temporary impairment of their functions as a result of transient interference with their blood, lymphatic or nerve supply. During the course of the 75 operations, 6 parathyroid glands were removed accidentally but in every instance the removed gland was reimplanted in the sternomastoid muscle. The care exercised to identify these glands during operation was attested by the fact that examination of the thyroid glands after removal revealed only two parathyroids.

Changes Produced by Total Thyroidectomy. *Their Mechanisms; Clinical Measurements.* Marked reduction in the level of basal metabolism was a constant result of total thyroidectomy. The metabolic rate probably begins to fall quite shortly after the operation, but it requires from 3 to 4 weeks for it to reach a level about 20% below that present before the operation. It is not until such a level has been attained that lasting beneficial results are to be expected,[16] although some relief of symptoms is observed frequently before this has been accomplished. It has been shown[5] that there is a close relationship between the observed improvement of the patient's circulatory state and the extent of fall in his metabolic rate. The metabolic level continues to fall and may reach to well below −40%.

The symptoms and signs of myxedema appear at levels below about −30%, and increase in severity more or less in proportion as the level falls below this point. The unpleasant and possibly harmful symptoms of myxedema can be controlled more or less completely by the administration of thyroid. The dose required seems to lie between 8 and 32 mg.

(gr. $\frac{1}{8}$ and $\frac{1}{2}$). Too large doses defeat the primary purposes of the thyroidectomy and may induce the return of cardiac symptoms, both those of failure and those of angina. The optimum level for the maintenance of the metabolic rate appears to lie at about −25%, varying slightly in different patients and determinable only by trial under close observation.

It has already been mentioned that Blumgart and his colleagues[5] had found a retarded rate of blood flow in cardiac patients who were suffering from congestive failure. Such patients were also observed to show an increase in the rate of blood flow when their symptoms of failure were relieved by medical treatment. Studies of the velocity of blood flow following total thyroidectomy in a group of patients previously suffering from congestive heart failure showed that the velocity of flow remained slowed, yet these patients were largely or completely relieved of their previously intractable heart failure. The mechanism underlying the relief of failure must therefore have been that of the reduction of the metabolism of the tissues, including the heart, to a level at which the diminished velocity of blood flow was adequate to meet most or all of the tissue requirements. In other words, while the heart is not able to accomplish increased work as a result of thyroidectomy, the reduction in the tissue demands by virtue of the lowered metabolic rate may be sufficient to restore the balance between the heart's capacity and the work (blood flow) required. In some instances it was shown that the work demanded of the heart had been reduced by the lowered metabolism to a level below that of the heart's capacity. In such patients actual cardiac reserve had been reëstablished to a limited degree by the thyroidectomy.

Exercise tolerance tests applied under standardized conditions before operation were repeated at various intervals after operation and their results confirmed both the clinical impressions that the patients had been largely relieved of congestive failure and the belief that the demands upon the heart had been diminished and its reserve increased. Significant improvement in the response to this test was observed even when the patient was retested only a few days after getting out of bed, and before his muscular tone could have been raised by increased physical activity. At this early date the basal metabolism had shown only a moderate degree of reduction, and as it fell to lower levels the patient's circulatory response to the exercise test was seen to improve, sometimes to a remarkable extent. With this measureable improvement in tolerance for exercise the patients observed less and less fatigue, diminished dyspnea, and other subjective manifestations of a restoration of cardiac compensation.

Diminished vital capacity of the lungs is a nearly constant concomitant of congestive failure.[22,23] Similarly, Blumgart[24] and associates have shown that the vital capacity is much lowered in the presence of the lowered metabolism of spontaneous myxedema although such patients were free from congestive heart failure. When, therefore, the vital capacity following total thyroidectomy was found to be increased in some patients and unchanged in others, both groups being similarly relieved of their previous respiratory symptoms, the divergence was readily explained. On the one hand the relief of heart failure tended to restore a greatly reduced vital capacity to normal, on the other the

fall in metabolic rate responsible for the relief of failure tended to reduce the vital capacity. The change which actually may be found in any given patient must, therefore, be the resultant of these two opposed influences.

The blood pressure in congestive failure was not significantly or constantly influenced by total thyroidectomy. Alterations in the electrocardiographic findings were frequent and quite in line with the alterations previously observed in spontaneous myxedema.[25] The outstanding changes were those of lowered voltage of the *Q–R–S* complexes and less frequently lowering in the amplitude of the *T*-waves, or their flattening. Ectopic premature beats were observed to disappear in several patients. They returned in one when the basal metabolism was raised by the administration of thyroid, and again disappeared upon its discontinuance.

One of the most striking alterations observed by the patients has been the frequent, prompt and complete relief of the pains and aches in the chest which often accompany congestive heart failure. These diminished and then disappeared in proportion to the fall in the basal metabolic rate. Recurrent hemoptysis was also relieved in several patients. Despite the relief of the signs of congestive failure and the marked effects upon recurrent hemoptysis, total thyroidectomy has not been followed by encouraging or consistent results so far as the control of paroxysmal dyspnea is concerned. The explanation of this failure is not clear.

Patients with the anginal type of cardiac failure seemingly are more constantly and more greatly benefited by total thyroidectomy than are those manifesting congestive heart failure. A group of such patients has been subjected to a series of carefully controlled observations prior to total thyroidectomy and at various times subsequent to that operation. It was observed that the relief of anginal pain in a number of patients followed immediately after the operation. In this group the relief was evidently not attributable to alterations in the thyroid function and in basal metabolism as these require from 3 to 4 weeks for their development. The mechanism of this early relief of anginal pain was investigated by Weinstein and his associates[26] who found that the pain and the hyperesthesia and hyperalgesia of the chest might all be relieved within as little as 2 hours following completion of the operation. They concluded that these immediate effects could be explained only on the basis of the severance during the operation of afferent nerve paths from the heart. That it was not due to the functional blocking of these paths as a result of local anesthesia or of their depression from trauma or postoperative inflammatory reactions was evident from the fact that the relief persisted. The explanation was further confirmed by demonstration of similar but strictly unilateral relief obtained in anginal patients subjected to hemithyroidectomy. The degree of relief thus obtained was pronounced and sometimes complete, as confirmed by the results of the comparative study of the response to a standardized exercise tolerance test repeated under controlled conditions. The relief was found to be essentially identical with that following cervical sympathectomy and paravertebral alcohol injections. In patients subjected to hemithyroidectomy the pain tended to reappear after periods of from 3 to 6 weeks.

Patients subjected to total thyroidectomy frequently showed both

immediate and permanent complete relief of all anginal pain and hyperalgesia of the chest. In such patients, however, a second mechanism of the relief of pain was introduced. This was brought about by the lowering of basal metabolism and the restoration of the normal relationships between heart work and blood flow. As previously pointed out, this mechanism generally begins to come into play after 3 to 4 weeks following thyroidectomy. In the patients studied, this mechanism was found generally to overlap that responsible for the immediate control of pain so that there was no subsequent recurrence of pain even when the standardized exercise tests were repeated, the amount of effort being markedly increased.

Further studies by Eppinger and Levine[27] showed that the response to the injection of adrenalin[28] was either greatly diminished or completely abolished immediately after thyroidectomy, thus adding confirmation to the observations of Weinstein and his associates.

Shambaugh and Cutler[29] carried out experimental studies on dogs in which they endeavored to test the effects of total thyroidectomy upon the production of pain by coronary constriction according to the method of Sutton and Leuth.[30] They found that thyroidectomy did not alter the pain response caused by this mechanical interference to coronary blood flow and they suggest that the beneficial effects of total thyroidectomy in man may be attributable to an interference with the thyroadrenal mechanism. They believe this to be especially likely as the explanation in view of the observations of Levine and his associates[28] just cited.

Miscellaneous and Collateral Studies Following Total Thyroidectomy. The development of myxedema was an expected consequence of total thyroidectomy. That myxedema may, itself, lead to cardiac enlargement, loss of heart efficiency, and even to congestive heart failure has been pointed out by Zondek,[31] Fahr,[32] Tung[33] and others.[25] The true "Myxedema Heart" appears to be relatively infrequent and signs of congestive heart failure as a result thereof are apparently rare.[34,35] Cardiac enlargement, diminished excursion of the chambers as seen fluoroscopically, and lowered potential of the Q–R–S and T waves of the electrocardiogram occur not infrequently. Their precise mechanisms of production remain debatable.

Davis[36] and his associates, therefore, studied the effects upon the heart in 37 patients upon whom total thyroidectomy had been performed. Symptoms and signs of myxedema developed after periods of 3 to 8 weeks following thyroidectomy and were readily controlled by small doses of thyroid extract. In a group of 22 patients operated upon for the relief of congestive heart failure the development of myxedema was accompanied by some enlargement of the heart teleoroentgenogram in 15; there was no change in 3 and slight decrease in size in 4 patients. The largest increase in size amounted to 2.7 cm. in the total transverse diameter, the greatest decrease to 1.4 cm. Among 11 patients with previous angina pectoris, 8 showed similar increases and 3 showed no change in transverse cardiac diameter. The changes in heart size were studied in relation to the progress and extent of the hypothyroidism on the one hand, and on the other to the alterations in signs and symptoms of heart failure. It was found that in the angina cases the alterations in heart size and in electrocardiographic voltage

ran parallel to the degree of the hypothyroid state. In the group which had previously had congestive failure there was no such relationship, the alteration in the size of the heart being the result of two opposing factors: diminution in heart size resulting from relief of congestive failure and enlargement of the heart due to myxedema. If the level of basal metabolism be kept at about −30% there seems to be little or no tendency for the signs or symptoms of hypothyroidism to progress.

In view of the established relationship between the level of thyroid activity in thyrotoxicosis and spontaneous myxedema and the level of the blood cholesterol content, studies were carried out to determine this relationship in the group of patients subjected to total thyroidectomy.[37] The results showed that the level of cholesterol rises as the basal metabolic rate falls and parallels more or less closely the appearance of clinical signs of hypothyroidism. Such changes begin to become appreciable within about a week after operation and are marked by the end of the first month. Although the basal metabolism does not fall significantly after the first month or 6 weeks, the cholesterol level continues to rise along with progression in the clinical signs of hypothyroidism. Clinical symptoms of hypothyroidism usually appear at blood cholesterol levels of about 300 mg. per 100 cc. and a basal metabolism rate of −30%. The administration of small doses of thyroid extract not only causes an elevation in the depressed level of basal metabolism but diminishes the cholesterol content in the blood.

Means and Lerman[38] point out from their prolonged clinical observations that patients with spontaneous myxedema may be maintained in excellent health for many years by the appropriate use of thyroid extract. Such patients have naturally a more even level, though greatly depressed, of basal metabolism than do normal patients and it is possible in such patients so to gauge the administration of thyroid as to control both the symptoms of myxedema and to maintain almost any desired level of basal metabolism. Between the levels of −20 and −30 such patients show generally but slight symptoms while, if the metabolic rate be elevated to about +10, symptoms of hyperthyroidism may make their appearance. A daily dose of 32 mg. ($\frac{1}{2}$ grain) of thyroid will maintain the basal metabolic rate at about −20 in the average myxedematous patient. Their studies also showed that a long period of time is required for the development of cachexia.

In the present series of patients with artificial myxedema there has been to date no evidence of development of progressive arteriosclerosis. Similarly, while many patients have shown a slight fall in both the numbers of red cells and the hemoglobin percentage, such changes have not been progressive nor have they resulted in symptoms which have required the administration of iron for the control of the anemia.

The metabolism of sugar was investigated in a group of these patients by Gilligan[39] who found it to be essentially uninfluenced as a result of the induction of hypothyroidism in patients whose pre-operative sugar metabolism had been normal. The production of hypothyroidism in a diabetic patient and in a patient who had hyperthyroidism resulted in marked decreases in hyperglycemia produced by the ingestion of glucose. Extending this study, Abrams and Gilligan[40] found that in non-hyperthyroid and non-diabetic patients the development of hypothyroidism following operation was without influence upon their

response to the injection of 20 units of insulin. Furthermore, the evidences of mild hyperinsulinism occurred at the same levels of blood sugar both before and after the development of hyperthyroidism. They conclude that the response of the sympathico-adrenal system is normal in these patients and that no antagonism exists between the internal secretion of the normal thyroid gland and the pancreas.

Hypoparathyroidism. Among 73 consecutive patients upon whom total thyroidectomy had been performed none showed either spontaneous spasm in the extremities or tetanic convulsions.[41] Twelve (17%) showed slight signs of mild hypoparathyroidism in 10 of whom these were transient, lasting for less than 2 weeks. The symptoms were limited to various degrees of paresthesia, to the appearance of Chvostek's and Trousseau's signs and slight but inconstant diminution in the level of serum calcium without consistent or frequent rise in inorganic serum phosphorus. The administration of calcium chlorid and an abundance of milk generally controlled the symptoms promptly. Calcium lactate or gluconate was used where the patient did not tolerate calcium chlorid. In the 2 patients who showed a persistent mild hypoparathyroidism, the symptoms could be controlled successfully by the combination of viosterol with a high calcium intake.*

Summary of Results. *Present Criteria for the Selection of Patients; Additional Incidental Observations.* Blumgart and his associates[42] have analyzed the results of total thyroidectomy performed on a group of 75 patients suffering from chronic heart disease without clinical evidence of thyrotoxicosis and in whom the ablated thyroid glands were proved, upon examination, to have been normal. All of the patients had been long incapacitated despite all efforts at relief by recognized therapeutic measures. Fifty of the patients suffered from chronic recurrent congestive failure. In 29 of these the failure was due to rheumatic heart disease and in 17 to arteriosclerotic heart disease with or without hypertension. There were 2 cases with congenital heart disease and 1 each of syphilitic heart disease and cor pulmonale. The ages ranged between 18 and 69 years. The sexes were equally represented.

The degree of clinical improvement produced by the operation was judged by changes in the usual clinical signs of congestive failure such as pulmonary congestion, orthopnea, edema, cyanosis and the like as well as by the patient's responses to various functional tests. Twenty-four have maintained compensation sufficiently to be able to work for periods varying from 2 to 18 months. In 6 congestive failure recurred temporarily but responded to the usual methods of treatment. There were 6 operative deaths and 6 deaths occurred at periods too late to be attributable directly to the operation. Two patients were not benefited by the operation. Of the compensated cases, 8 have maintained their compensation for periods of a year or more. Among those showing recurrent failure the cause could not be determined in 3. The recurrence was due to overactivity in 1; to the reappearance of bronchial asthma and to the discontinuance of digitalis in 1 each. Among those who died

* [Note: I have been observing one of these patients who, after nearly 18 months remains on the borderline of hypoparathyroidism which necessitates his receiving a high calcium intake and a small daily dose of parathyroid extract, without which he promptly approaches having tetany.—Editor.]

between 3 weeks and a year postoperative, death was due to cardiac failure in 3; to cerebral embolus and pulmonary edema in 1 each and to unknown causes in the sixth. Of 32 patients with angina pectoris who were operated upon, in 19 angina was the major disabling factor. In 5 of the remainder cardiac asthma was of first importance and in 8 congestive failure. The anginal syndrome was sufficiently pronounced in 25 of this group to permit the evaluation of the effects of operation. In this controlled group, 8 have shown no recurrence of angina over a period of 3 to 18 months in spite of marked physical activity.* Five previously completely incapacitated have had only occasional attacks since operation and their range of activity has been markedly increased so that they could return to some form of occupation. In 2 patients anginal attacks have recurred after a period of complete relief in the one following an accident, in the other, a coronary occlusion. Marked increase in the level of metabolic rate produced by thyroid administration caused recurrence of angina in 3. One patient in the anginal group died following coronary occlusion 3 months after operation after a period of complete relief from angina. All but 4 showed more or less marked increase in their tolerance to exercise. These 4 have attacks of angina in response to exercise which have been quite uninfluenced by operation and have been unable to resume any form of work. Three of these 4 unsuccessful cases were patients having low preoperative basal metabolic rates ranging between -19 and -24%.

Experience to date indicates that the best results from total thyroidectomy are to be obtained in those patients with chronic congestive failure due either to rheumatic or hypertensive arteriosclerotic processes who can be restored to compensation when at rest in bed. Those who do not respond to rest in bed in conjunction with the customary methods of medical treatment, on the other hand, are likely to derive relatively little benefit from the operation and are also such poor surgical risks as to make the operation too hazardous. Since the basic theory underlying this method of treatment rests upon a restoration of the normal balance between the heart work and basal metabolism, the choice of patients should for the most part be limited to those whose pre-operative metabolic rate is not more than about 15% below normal standard. Experience has shown that patients falling below this level show very little benefit. Similarly in the case of the anginal group of patients those with significantly depressed basal metabolism show little improvement and the best results are obtained among patients whose attacks of angina occur upon very mild exertion but not when the patient is

* [One of these patients has been studied recently in our clinic. He was operated upon in November, 1933, with complete relief for several months and a great increase in his exercise tolerance without the induction of angina. For many months past he has, however, suffered greatly from the discomforts of his myxedema at a metabolic level of about -25%. If his dose of thyroid is increased and his metabolism thereby elevated just enough to make his myxedema bearable he suffers from his angina about as severely as before operation. Even with a -23% level of metabolism he has angina on cool days, on climbing slight grades, and has been quite unable to work. Tested on the standard steps in a warm room anginal pain now returns after the same amount of effort which was required just prior to operation. The patient stated that if he had known in advance what the discomforts of moderate myxedema were, he doubts if he would have undergone thyroidectomy. In his case it is practically impossible to adjust the administration of thyroid so that both his angina and his myxedema are bearable.—EDITOR.]

at rest. If a sufficient period of time be allowed to elapse following its occurrence the previous development of coronary occlusion is not a contraindication to thyroidectomy. No patient should be operated upon who shows evidences of active infection, recent vascular accident, pronounced renal disease or the evidence of active rheumatic disease.

Certain changes have come about in the pre-operative preparation of patients in addition to those already cited. Not only should every effort be made to restore compensation but in patients suffering from auricular fibrillation, it seems advisable to use rather larger doses of digitalis than otherwise just before operation so as to make sure of controlling ventricular rate. Whatever sedatives may be needed should be well tried out during the pre-operative period of study to determine the patient's reaction and to exclude the presence of idiosyncrasy. As little sedative as possible should be used during the operative period. The employment of oxygen therapy may diminish operative results in a certain proportion of cases.

Postoperative Medical Management. Except for the necessity of regulating the level of hypothyroidism, there is generally very little medical care required following operation in patients with angina pectoris.[43] Many of these patients may be allowed to be up as shortly as 48 hours after operation and may even be discharged from the hospital within a week to 10 days. It is, however, better to retain such patients under hospital control sufficiently long to see them through their adjustment periods and if possible to establish appropriate control of their metabolic level by thyroid administration.

Patients operated upon for the relief of chronic congestive heart failure generally require more prolonged postoperative convalescent care. Where compensation can be restored completely before operation, the period of postoperative convalescence rarely needs to exceed 3 weeks but the usual regimen for the control of chronic heart failure should be continued. There should be a gradual adjustment in the amount of physical effort permitted. The administration of digitalis should be continued in doses appropriate to the needs of the individual patient. This is especially important during the first 4 to 6 weeks, the period before hypothyroidism becomes well established. In all cases, but especially in those with previous congestive failure, the resumption of physical activity as well as the degree of activity allowed should be gradual and should be permitted only under close supervision. In this group with previous congestive failure, Mixter, Blumgart and Berlin[16] recommend that the patient be kept for the most part at rest in bed until basal metabolism has fallen to at least -20% in order to protect the patient against the recurrence of congestive failure from the too prompt resumption of activity. The management of the cardiac condition in such patients is generally the same after operation as before so far as drugs are concerned and it is commonly necessary for such patients to continue the use of digitalis especially those showing auricular fibrillation.

Comment. The introduction of a new therapeutic agent or procedure, especially when its results appear dramatic, is likely to be received with excessive and often unwise enthusiasm. The critically scientific attitude of the proponents of total thyroidectomy, together with their manifold precautions in the selection and care of otherwise seemingly

hopeless cases so imbues all of their papers with conservatism that an excess of unbridled enthusiasm may have been prevented. If this be true, then the lapse of time should permit that controlled study of total thyroidectomy which must be undertaken on a purely experimental basis before it can be safely accepted, rejected or admitted into rational therapeutics on a narrowly yet soundly restricted basis. It is certainly not yet the time to attempt conclusions as to its true place as a remedial measure. Much more knowledge concerning all of its results must be accumulated before that can be done. At present it should continue to be regarded as an experiment of some promise.

Among the many problems raised, the following seem of most immediate importance. Are the results in cases of congestive failure enough better than those of the best medical treatment[44,45] to justify either the risks involved, or the very considerable handicaps and discomforts of myxedema? What proportion of patients with congestive failure cannot be maintained in a reasonably satisfactory condition by the best possible medical treatment? It would appear to be extremely small if those be excluded in whom the heart lesions are inevitably progressive. If thyroidectomy is of real benefit in this small group, can we develop still better and more accurate methods for their recognition? Is there any evidence to suggest that the progress of the underlying disease of the heart or arteries is altered by thyroidectomy? Does artificial myxedema induce vascular changes like those found in the spontaneous disease, or does it promote the advance of such changes as may already be present? In what percentage of patients can thyroidectomy be anticipated to maintain cardiac compensation for more than one year? Is the duration of reasonably comfortable life materially prolonged?

The results of thyroidectomy appear to be somewhat better and more likely to be secured in patients with angina and in those with cardiac asthma than in other types. In some the results have been truly dramatic. Can we improve our present methods for selecting patients who will fall in this latter group? Many of the problems are the same for the anginal cases as for those with congestive failure and do not need repetition. It remains to be determined what percentage of anginal patients will be relieved for as long as one year. It is not always possible to control the sufferings of myxedema without reinducing angina. In what proportion of patients is such an adjustment feasible? Is the comfortable life of the anginal patient significantly prolonged? Is life expectancy lengthened?

Space prevents further comment along these lines, but it must be pointed out that cardiac failure occurs spontaneously in persons with low basal metabolism and even in the presence of spontaneous myxedema. It seems justifiable, therefore, to raise the question: Is total thyroidectomy a procedure of more than temporary value?

Whatever the ultimate status of total ablation of the normal thyroid gland may be proved to be, its proponents deserve high praise for the theoretical soundness of their conceptions, their originality, their caution and their courage.

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(Titles have been omitted for sake of brevity.)

RADIOLOGY

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RADIOTHERAPY.

THE specific sensitiveness of each kind of cell looms up as the dominant single fact in radiology, and, Desjardins[1] asserts, if reaction time is taken as a criterion, deserves to be recognized as a law. The sensitiveness peculiar to each kind of cell appears to be related chiefly to the natural life cycle. Thus the lymphocytes, the metabolic cycle of which among human cells is the shortest, are the most radiosensitive, while the nerve cells, the life cycle of which is the longest, are the most resistant to irradiation. The notion that pathologic cells are more radiosensitive than normal cells of the same kind is valid only to the extent that the rate of mitosis of cells is affected by the pathologic disturbance. The significance of this factor, therefore, is limited to tumors and to processes of which cellular hyperplasia is an important feature. Such influence is small as compared with the specific natural susceptibility of each variety of cell and with the age or metabolic status of the cells. Cellular radiosensitiveness, therefore, is the natural reactivity of different kinds of cells to a given quantity of radiation of a certain quality (average wave length) when the cells are exposed in a certain way (scheme of irradiation) as estimated clinically by an experienced radiologist. Radiosensitive tumors are growths the sensitiveness of which is greater than that of the skin; moderately radiosensitive tumors have a sensitiveness approximating that of the skin, and radioresistant tumors one less than that of the skin. Certain factors are known to cause variations in the radiosensitiveness of neoplasms, among them may be mentioned impairment of blood supply, disturbance in anatomic relations, acting mainly by interfering with the circulation and lymphatic drainage and by inducing the formation of connective tissue, cachexia by reduction of the patient's resistance, sepsis, the influence of which is not understood, and previous irradiation. Lessened radiosensitiveness from previous irradiation probably results from the gradual secondary proliferation of connective tissue which follows the destruction of malignant cells, as well as from the increasing inhibition of mitotic activity of the malignant cells from repeated irradiation and also from diminishing blood supply. Numerous attempts to increase the sensitiveness of tumors have been made by injecting intravenously various dyes and other substances, but the results have not been sufficiently striking and conclusive to command wide acceptance. Desensitization of the skin by reducing the circulation through the cutaneous vessels by pressure during the time of irradiation has not been conspicuously successful.

Landauer,[2] in reviewing the physical aspects of various qualities of radiation, feels that only that radiation which is absorbed produces any biological reaction. The greater the quantity of radiation absorbed, the greater will be the beneficial effect. The harder the radiation, the greater the quantity absorbed as it is measured from depth dose measurements. Craver and MacComb,[3] reviewing their experience with the Heublein method of continuous irradiation at low intensity, over periods of several days to 3 weeks, of the entire body, with target-skin distance of over 5 meters, consider it a valuable addition to the treatment of several radiosensitive tumor processes, such as leukemias, lymphosarcoma, Hodgkin's disease and multiple myeloma, and that its results in the treatment of chronic lymphatic leukemia and pseudoleukemia are superior to those obtainable by local irradiation. They found it to be of only slight value in the treatment of radioresistant tumors.

Elliott and Jenkinson[4] report a case of ulcerations of the stomach and small intestine following Roentgen therapy, with perforation and death. Kaplan[5] very comprehensively reviews the problem of the care and treatment of chronic cancer cases. He groups these as (1) those for whom something radical can be done in the form of intensive treatment, and (2) those for whom only such measures can be undertaken as will relieve mechanical or functional disturbances of normal body condition. The chronic cases are divided into those which may be treated (*a*) as ambulatory cases in the routine follow-up clinic, (*b*) in the home, and (*c*) in the hospital.

Eller[6] asserts that the therapeutic potency of Roentgen rays is well established and leads the field of dermatological physical therapy. In some cases, such as mycotic infections (ringworm and favus) of the scalp, keloidal formations and hyperidrosis, Roentgen rays alone can improve the condition. In other conditions, such as plantar warts, beard infections and epitheliomas, this method of therapy is most valuable. In psoriasis, eczema, lichen planus, ringworm of the glabrous skin, certain epitheliomas, etc., Roentgen rays are used in combination with other medical and surgical procedures with advantage. Radium, even though it is not used as extensively as Roentgen rays, is often a great aid to the dermatologist. It has a distinct advantage in the treatment of certain lesions, such as epitheliomas or keratoses located near the inner canthus of the eye or alæ of the nose. Also radium gives by far the best cosmetic results in angiomas and certain other vascular nevi.

Grenz rays are Roentgen rays of extremely long wave length (8 to 10 kv.) and are useful in: multiple flat epitheliomas of the skin; verrucæ planæ of the bearded region or other areas of the skin; localized neurodermatitis; eczematous conditions of the scalp, eyebrows and eyelids; certain cases of dermaphytosis of the glabrous skin; sarcoids; and superficial lesions of lupus vulgaris. Roentgen rays are used in dermatology for the following: Conditions in which it is desirable to epilate hair temporarily, such as tinea capitis, favus, sycosis and nevus pilosus; to reduce the activity of the sebaceous glands, as in acne vulgaris, acne rosacea and seborrhea; to inhibit the function of the sweat glands, as in hyperidrosis, bromidrosis, chromidrosis, pompholyx and hydrocystoma; to change the metabolism of the regional cells or produce an environment that is less favorable for the growth and reproduction of bacteria and fungi, as in skin tuberculosis, sycosis vulgaris, fungus infec-

tions, selected cases of furunculosis, acne varioliformis, etc.; and for the relief of pruritus. Most superficial therapy is done with unfiltered radiation. Only a few dermatoses are treated by filtered Roentgen rays. In sufficient doses, soft Roentgen rays can produce a caustic and destructive effect. The dosage of Roentgen rays has been based upon the skin unit, *i. e.*, the dose required to produce a temporary epilation of the hair of the scalp. Translated into roentgens, one skin unit is equivalent to about 350 r. Variations in susceptibility to irradiation play an important part in the production of sequelæ. Telangiectases subsequent to irradiation usually occur within 2 years, although they may not appear until the third, fourth or even the fifth year.

In radiation therapy of cancer of the skin, Grier[7] advises irradiation as the treatment of choice; unfiltered radiation is preferable, and massive doses produce the best results in his experience. Seven times an erythema dose is the minimum that should be used. He bases dosage on the physical characteristics and the history of the lesion rather than upon microscopic findings. An analysis of his own cases convinces him that the most common cause of failure or recurrence is underdosage. In the treatment of psoriasis in Bellevue Hospital, Rosh[8] has used Roentgen irradiation of the sympathetic nervous system, which at the same time affects the thymus tissue. The application of high voltage Roentgen rays to the spine at those levels which correspond with the nerve supply to the affected parts first increased the itching, but this was soon followed by complete cessation of this symptom. After 3 weeks' treatment the color faded from the center of the affected areas, the scales became loosened, and the surrounding infiltration in the skin was diminished. In most cases a second series of treatments was given after a period of 6 to 8 weeks, during which time a majority of the areas were replaced by a brownish pigmentation. Complete disappearance of the lesions occurred in 3 to 6 weeks after the administration of the last treatment. In some persistent cases, a year elapsed before the body was free from psoriasis.

In the treatment of acne vulgaris with Roentgen rays, MacKee and Ball[9] reported 60% of their patients clinically cured with one course of treatment, *i. e.*, in 4 months or less. Recurrences totaled approximately 11%. Without Roentgen ray treatment there were approximately 40% failures; with Roentgen ray treatment the failures amounted to about 5%. In their experience, radiotherapy offers the most certain method of obtaining a clinical, and even a permanent cure, in the shortest time. Morrow and Taussig[10] discuss radium dosage and technique in benign lesions of the skin. In their experience there are but few conditions responding to radiation in which the Roentgen ray is not at least equal to radium. Radium is generally considered superior, or at least equal, to the Roentgen ray and other forms of therapy in vascular nevi, nevus flammeus (port-wine mark), nevus vasculosus (strawberry mark), cavernous hemangiomas and fleshy nevi; none of these should be treated by Roentgen therapy. Roentgen radiation is usually preferred in keloids. Roentgen rays and radium are equally efficacious in the treatment of verrucæ; the same applies in synovial cysts, and radium is preferable for epulis in the vascular type occurring between the teeth; the other types are most satisfactorily treated by electrothermic surgical methods. The greatest danger in the use of radium in the therapy

of dermatologic conditions is that of late sequelæ; telangiectases, atrophy, keratoses, and even malignancy.

Pfahler and Vastine[11] state that if all the knowledge that is now available is utilized skillfully, practically all cancers of the skin can be prevented and, if they occur, and are treated reasonably early while the disease involves only the skin, they should be cured. They stress the treatment of precancerous lesions; moles, particularly the pigmented moles, should be removed; likewise, all warts and particularly senile warts, any abnormal crusts, fissures or chronic ulcers. The fear of operation often keeps a patient from coming to a physician; radiotherapy eliminates this fear, and radium, Roentgen rays, electrocoagulation or surgery, separate or combined, may be discussed later with the patient, as the individual case suggests.

The rate of recuperation of human skin following irradiation was studied by Duffy *et al.*,[12] and they considered the skin to be an obvious indicator of the degree of damage produced and the rate of recovery in tissues an important factor in all methods of irradiation. Dividing the procedures into the three fundamental types: massive, fractional and saturation dosage, *i. e.*, where the maximum effect is obtained through a single exposure to radiation (massive); where the maximum effects are obtained by the gradual administration of small doses (fractional); or the maintenance for a certain time of a biologic effect already present, by the addition of smaller doses (saturation). Using the gradual fading of the reaction after treatment as an evidence of recuperation of tissues from radiation damage, they determined the quantity of radiation necessary to produce equal skin reactions in single and divided doses of 200 kv. Roentgen rays filtered by 0.5 mm. of copper and 2 mm. of aluminum, using the threshold erythema as a standard reaction for comparison. The threshold erythema dose for a single exposure was 525 Roentgens; for equal amounts given at intervals of 24 hours, 400 Roentgens for each exposure and, for equal amounts given at intervals of 48 hours, 425 Roentgens for each exposure. They found the skin recovered 69% of the immediate damage in 24 hours and 76% in 48 hours.

Howes[13] presents a group of cases of all types of epitheliomas of the skin and lip treated by one massive dose or divided doses on consecutive days, and considers his results comparable with other accepted forms of treatment. Widmann[14] comments that the popularity of irradiation procedures for carcinoma of the lip has become international, and attributes this to the relative simplicity of administration, as well as the speed and economy with which result is obtained. There is practically no treatment mortality, no risk of hemorrhage or infection, and the cosmetic results are excellent. His best results were obtained in small lesions and with adequate treatment of lesions of short duration. He found no evidence to indicate that irradiation will consistently effect regression of metastatic nodes. Surgical excision seemed justified of isolated, freely movable nodes that develop after apparently adequate high voltage Roentgen ray or radium pack treatment. Prophylactic irradiation of the cervical node region is warranted by his experience. He favored free and wide electrodesiccation in conjunction with radium or Roentgen rays in small lesions.

Kaplan *et al.*[5] discuss the protracted external irradiation method in

the treatment of carcinoma of the mouth and throat, and compare their results with Roentgen rays, the 5-gram pack and the small radium pack. Martin and McNattin[15] compare the results in the treatment of cancer of the pharynx, tonsil and extrinsic larynx by divided doses of external radiation with the Pfahler saturation technique, a fractional dose method based largely on the theory that there is a loss of radiation effect at a definite rate and that by daily repetition of a certain percentage of the original dose, this loss is replaced so that the original effect is maintained or prolonged for a desired period; and that of Coutard, which is based on the theory that the effect of multiple daily doses of external irradiation is cumulative, and that there should be a steadily increasing radiation effect brought to a climax after 2 to 4 weeks of treatment. The total doses employed by Coutard are much larger than those given by any other method of external irradiation. Such intense biologic effects as a blistering or epidermicidal reaction of the skin and a membranous mucositis in the pharynx are deliberately produced as a requisite to the accomplishment of a lethal effect on the underlying tumor. Coutard demonstrated that these biologic effects on the skin and mucous membrane invariably healed without difficulty. By such repetition of daily doses there is a greater differential effect as between normal and neoplastic tissue than if one or only a few massive doses are given at longer intervals. They feel the divided dose technique for the treatment of pharyngeal cancer, or cancer in general, has not been as widely emphasized as its merits deserve. The technique of the Coutard method is given in detail. Lenz *et al.*[16] review a series of cases of epithelioma of the pharynx and larynx treated by a modification of the Coutard method. Pfahler[17] has tabulated his results in the treatment of cancer of the mouth by surface and interstitial irradiation. His custom is to begin with radium packs or high voltage Roentgen rays externally to control at the beginning the spread of the disease. This is followed almost immediately by local surface applications of radium inside the mouth, usually alternating the local application one day with an external application the next, so that the patient does not become too much disturbed by one form of treatment. The applications are made successively on all sides of the tumor area, so that all parts of the tumor tissue shall receive from 6 to 10 erythema doses, counting the external radiation. As director of a state institute founded primarily for the purpose of research concerning the causes and the treatment of cancer and allied diseases, working with a personnel consisting of a surgeon, a radiotherapist, a physicist and a pathologist, supplemented by other specialists interested in cancer therapy, Simpson[18] is convinced that a large percentage of lip and intraoral cancer cases have established metastases which are not demonstrable. The consensus of opinion in his group is that in most cases radiation is the preferable method of treatment for metastatic deposits in the neck. He discusses their results with implantation (gold seeds of radon), external radiation (Roentgen ray) and radium in such cases.

Pfahler and Kapo[19] review the results in the Roentgen treatment of 333 consecutive cases of cervical adenitis. Following a brief review of the anatomy of the lymphatics of this region, they discuss the more common causes of cervical adenitis and the differential diagnosis. They, and their surgical colleagues also, were convinced of the superior value

of Roentgen irradiation in the treatment of cervical adenitis. The treatment can ordinarily be given without hospitalization; the majority can be cured with from 2 to 4 treatments; and with present technique, atrophy and telangiectases can be avoided. Butler and Woolley[20] feel that Roentgen therapy has a definite place in the treatment of chronic paranasal sinusitis in properly selected cases. There is no damage to normal structures when properly applied, and failure of Roentgen ray therapy in no way interferes with subsequent surgical intervention, should this become necessary. Their results were better in cases given single, full doses than in those in which fractional dosage was employed.

Merritt and McPeak[21] reported 6 cases of cystic bone disease which were either entirely cured or definitely benefited by Roentgen therapy applied over the parathyroid region. Fried[22] considers syringomyelia as particularly suitable for Roentgen therapy because the pathologic structure of this disease is highly responsive to the action of the rays. Radiation can halt the inflammatory process in nerve cells and fibers similarly to its action in any other inflammation. In order to obtain the best results it is necessary to commence treatment early in the course of the disease. When the condition has reached the destructive stage, radiation can still interfere with the process and preserve the residual function of the cord which has been retained in the tissue. When no definite improvement takes place by the end of the first series of treatments, a favorable effect can hardly be expected from further irradiation.

Brunschwig and Kandel[23] made studies to correlate the histologic changes and the clinical symptoms in irradiated Hodgkin's disease and lymphoblastoma involving lymph nodes, and to determine, if possible, the reason for the failure of irradiation therapy to eradicate the disease. They concluded that if Hodgkin's disease affected the entire reticuloendothelial system from the start, little more than palliation could be expected from irradiation therapy. If, on the other hand, the process is at first a local one, and if the involved group of lymph nodes is discovered early in the progress of the disease, intense local irradiation, with the object of completely sclerosing the lymph nodes, may offer a possibility of arresting the process. From the histologic standpoint, lymphoblastoma is more radioresistant than Hodgkin's disease. Irradiation of lymphoblastomatous nodes, if the process is of the more malignant type, may result in a reduction of size and some sclerosis; in the chronic cases the nodes are reduced in size, but not sclerosed.

In the discussion of radium dosage and technique in treatment of carcinoma of the breast, Taylor[24] states that the treatment of choice for operable carcinoma of the breast is radical surgery. In the treatment of inoperable and recurrent cases the chief dependence has been upon Roentgen therapy. Radium treatment was essentially palliative, and used as a part of a general plan of radiation therapy, most of which was delivered in the form of Roentgen rays. Following the methods of Geoffrey Keynes, selected cases were treated. Regression of the local process was secured in almost all cases, and seemed to be better than that secured with Roentgen treatment alone. Richards[25] presents a jacket which he devised to solve the difficulty of delivering to the curved surface of the thoracic wall, in the treatment of secondaries in

this region from carcinoma of the breast, a dose of irradiation which would be evenly distributed over the entire area and at the same time effective. The jacket was fitted to the individual patient and provision was made for the attaching of rows of radium needles, accurately spaced from each other, from the midline in front as far as thought advisable. Approximately 100 needles, 60 mm. in length, contain 3 mg. of radium element and having a wall thickness of 0.8 mm. of platinum (standard platinum iridium) were used and left in position from 90 to 100 hours. The reaction which follows is fairly severe, a first to second degree erythema with vesication, and requires very particular care in its treatment.

Baum[26] reports a case and presents a survey of the recent literature on radiation therapy in carcinoma of the bronchus. He includes a study of the end results in the literature of the surgical treatment of this condition, and concludes that irradiation is to be preferred in the treatment of lung carcinoma. Only comparatively early cases are suited for lobectomy; the insidious nature of the disease makes early diagnosis practically impossible; lobectomy carries a high mortality (20 to 30%); radiation by Roentgen ray or radium, or both, has no immediate mortality; and even if life is not prolonged by radiotherapy, the patient's suffering is greatly lessened, and what life remains is made more endurable.

Henry Schmitz[27] reviews a series of 662 cases of carcinoma of the female genitalia treated by irradiation. The number and per cent of the cases involving the vulva, vagina, cervix uteri, corpus uteri and ovaries are tabulated. Eighty per cent of the carcinomas were located in the cervix. The extent of the growth of carcinoma of the uterine cervix decides the rate of curability; the freely movable, clearly localized growths show from 80 to 90% good end results after a 5-year period. So he stresses the careful investigation of chronic cervicitis, low-grade chronic inflammations which frequently precede carcinoma, and follow-up of infections, abortions and lesions resulting from childbirth with adequate treatment of abnormalities to prevent cancer. Silent, early carcinomas found during these examinations, adequately treated, will achieve permanent healing in the majority of cases. Montgomery and Farrell[28] found the hopefulness of prognosis in carcinoma of the ovary was proportional to the grade of malignancy. The histologic findings of 22 cases were correlated with the gross pathologic appearances. The results of postoperative therapy were palliation of symptoms frequently, lessening of pain and recession of edema, with definite prolongation of life in many patients. Simpson[29] presents in detail the technique of treatment of cancer of the cervix with radon. He thinks radon has the advantage of being less bulky than radium, prefers the use of large quantities of radon, such as 1000 mc., for short periods of time to that of small quantities of radium for long periods of time; believes intrauterine treatment should be delayed until treatment against or outside the cervix has rendered it patent; that if the uterine canal has been once invaded, further intrauterine treatment should be delayed for a period of at least 6 weeks, and advises against the current practice of implanting the cervix.

Healy and Arneson[30] combined routine Roentgen irradiation for the distant pelvic involvement and radium for the cervical lesion, giving

the Roentgen ray cycle before application of radium in all but the earliest cases. This has seemed to be advantageous in diminishing the discharge as well as the bleeding, and in reducing the gross size of the primary lesion by causing the superficial, infected and friable tissues to disappear. As a result, there is also less swelling and induration in the surrounding tissues. In this way the cancer field is in much better condition to react satisfactorily to the application of radium, and usually the local and constitutional reactions are less severe. This report deals with an attempt to control parametrial disease by increasing the amount of external irradiation with Roentgen rays so as to obtain a greater intensity of radiation within the pelvic structures without causing severe damage to normal tissues. In the earliest cases radium treatment precedes the Roentgen ray.

The first important advancement in the treatment of carcinoma of the rectum was surgical, and for many years surgical intervention was the only method of treatment. With the advent of radium and Roentgen rays, however, the field of treatment has been extended, and radiotherapy in this field is destined to be of as much value as surgical treatment has been; from a combination of the two methods great benefits will be inevitable. With this introduction, Bowing and Fricke[31] present various tabulations of the situation and classification of rectal tumors, the age incidence, clinical data, index of malignancy, classification of the length of life by grade of malignancy, and a review of the procedures in 500 cases. They believe that therapeutic radiology, especially radium therapy, has a distinct place in the treatment of carcinoma of the rectum, anus and rectosigmoid. Preoperative radium therapy should receive special consideration and, when employed, should be followed by a period sufficiently long, probably 8 to 12 weeks, before surgical intervention is attempted. Radium therapy as a palliative procedure is of value, and inoperable and recurring lesions should be given at least one well planned treatment. The degree of palliation naturally varies, but nearly all the patients will be benefited somewhat. Radium therapy as a postoperative measure has a limited field of usefulness; all lesions of a high grade of malignancy at least should be treated. Roentgen therapy is of value, and with the increased voltage of the present-day installations, should become of greater value, especially in cases in which lesions are of the higher grades of malignancy. These authors, with Counseller,[32] have studied the results of treatment of carcinoma of the penis. Epithelioma of the penis is a slow-growing neoplasm which is inclined to remain superficial for a long time, to metastasize late and, when such metastases do occur, to affect the inguinal nodes. The slow growth and accessibility of the lesion render it amenable to surgical treatment and to irradiation with radium and Roentgen rays alone, or probably best in combination. In inoperable cases, irradiation alone accomplishes a great deal in the way of palliation.

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(Titles have been omitted for sake of brevity.)

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 18, 1935

Studies in the Mechanism of Kaolin Hypertension.—WILLIAM ALLEN JEFFERS, M. AUGUST LINDAUER and JOHN Q. GRIFFITH (Robinette Foundation University of Pennsylvania). Thorotrast will appear in the cervical lymph nodes of the normal albino rat, as shown by Roentgen ray, about 45 minutes after 0.02 cc. of the substance has been injected into the cerebellomedullary cistern.

Thorotrast, so injected, does not appear in the cervical lymph nodes even after a period of 10 days, if the animals have been shown to have peripheral arterial hypertension following a previous intracisternal injection of colloidal kaolin.

It is suggested that this peripheral hypertension is caused by the increased intracranial pressure. This increased pressure is thought to be due to a block in the channels for lymphatic absorption. The alternative suggestion, that it is due to a persistent meningeal reaction, is considered, but is thought to be unlikely because the leukocytosis in the spinal fluid following the intracisternal injection of kaolin is

present only for the first 3 days and subsides completely by the fifth day. On the other hand, the hypertension seldom appears before the fifth day and usually persists indefinitely.

The Action of Single Doses of Morphin Sulphate Upon the Movement of the Small Intestine in Man.—W. Osler Abbott and E. P. Pendergrass (Laboratories of Pharmacology and Radiology, and the Gastrointestinal Section of the Medical Clinic, University of Pennsylvania). Morphin was early observed by fluoroscopy to relax the small intestine, to depress its activity and to delay the motility of its contents. Subsequently balloons in small intestinal "loops" of dogs showed increased tonus and peristalsis. We have combined these methods in normal, intact human subjects. With orally administered balloons recording simultaneously from one or two points between pylorus and cecum, barium is given and the subject fluoroscoped.

Results. The duodenum, 2 minutes after 10 to 30 mg. of morphin sulphate is administered hypodermically, contracts forcibly, as shown by a disappearance of barium from the duodenal lumen and by strong compression of the balloon for 20 minutes. Then follows hyperperistalsis of brief duration and thereafter prolonged inactivity. Duodenal stasis and regurgitation, present earlier, disappear. In the ileum there is either slightly increased segmentation or no immediate response. Then the barium gathers into boluses, the gut dilating and becoming less active. The balloons show nothing save a slight transitory rise in tonus at 15 minutes, probably in part due to downward displacement duodenojejunal content. Activity diminishes thereafter. The jejunum reacts in a manner between that of the duodenum and the ileum. Subnormal activity may persist for 24 hours.

The Measurement of Serum Volume.—F. William Sunderman (John Herr Musser Department of Research Medicine, University of Pennsylvania). In the determination of the serum volume by the intravenous injection of vital red, there is evidence to suggest that complete mixing of the dye in the circulating serum does not occur for 20 to 30 minutes after the injection. If samples of serum are obtained under basal conditions at intervals of 30, 60 and 90 minutes after the introduction of the dye, a linear relationship is obtained which permits extrapolation to the moment of injection and the estimation of the concentration of dye that would have been obtained were complete mixing instantaneous. The quantity of dye injected is measured with precision by means of an especially constructed apparatus. The colorimetric readings are made on undiluted serum in a colorimeter having 2 chambers on each side and fitted with a green monochromatic filter. A simplified procedure requiring only 2 samples of blood is proposed for clinical studies. The procedure gives consistent, reproducible results in normal individuals and reveals differences beyond the normal range in some pathologic cases.

Nerve Impulses in Single Fibers of the Vertebrate Retina.—H. K. Hartline (Eldridge Reeves Johnson Foundation, University of Pennsylvania). Oscillographic records of action potentials in single optic nerve fibers of the frog's eye have been obtained from small bundles of fibers dissected from the anterior surface of the retina near

the head of the optic nerve. The discharge of impulses in such fibers, in response to illumination of that portion of the retina from which they come, shows considerable diversity, even among fibers from closely adjacent areas of the same eye. In certain of these fibers the response is similar to that in the optic nerve fibers of Limulus, showing an initial burst of impulses at high frequency, with subsequent adaptation to a lower level of steady discharge, which is maintained as long as the illumination lasts. In outer fibers, however, the initial burst of impulses is absent, and the discharge builds up slowly (over 1 or 2 seconds) to its steady value. Such fibers show an increase in the impulse frequency when the light is turned off ("off effect"). This is interpreted as post-inhibitory rebound. In another group of fibers it is the maintained discharge which is absent, and the only response is a short burst of impulses when the light is turned on. Such fibers may also show an "off effect," varying from a few impulses to a vigorous burst. In the fourth group of fibers no response at all occurs during illumination, but as soon as the light is turned off a vigorous discharge occurs, initially at high frequency, but gradually dying out. In some cases this discharge may take many minutes to disappear, and occasionally has been observed to break up into a series of rhythmic bursts of impulses. Re-illumination promptly inhibits the discharge in this group of fibers.

It is supposed that this diversity of function among the optic nerve fibers of the frog retina is due to a modification of the original sensory discharge by the neural elements intervening between the sense cells and the optic nerve fibers, and that the various types of discharge will find their explanation in the interplay of excitatory and inhibitory processes in these elements.

Correction.—In the article by Doctors Cohn and Lewis in this JOURNAL (April, 1935, issue) on page 478, lines 5 and 7 from the bottom, and page 481, lines 5 and 8 from the top, the word "weighing" should be "weighting." In the fourth line of the legend of Figure 16 (p. 473), after the word "noted," the word "especially" should be inserted.

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